(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 April 2003 (03.04.2003)

PCT

(10) International Publication Number
WO 03/026664 A1

(51) International Patent Classification[7]: A61K 31/506, C07D 401/14, 403/14, 405/14, 409/14, 413/14, 417/14

(21) International Application Number: PCT/US02/30836

(22) International Filing Date:
26 September 2002 (26.09.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/325,110 26 September 2001 (26.09.2001) US

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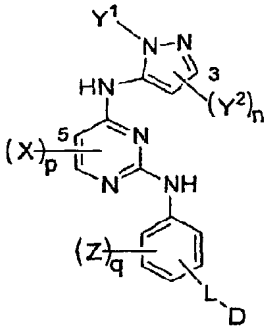
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

[Continued on next page]

(54) Title: 2-PHENYLAMINO-4- (5-PYRAZOLYLAMINO) -PYRAMIDINE DERIVATIVES AS KINASE INHIBITORS, IN PARTICULAR, SRC KINASE INHIBITORS



(I)

(II)

(57) Abstract: The invention provides novel substituted 2,4-diaminopyrimidine compounds (I). In formula (I), the variables are as follows. Y^1 represents H or C_{1-4} alkyl. Y^2 represents CF^3, C_{1-6} alkyl; C_{3-6} cycloalkyl; or phenyl optionally substituted with halogen, C_{1-4} alkyl, or C_{1-4} alkoxy. The subscript n is 0, 1, or 2. X represents halogen or C_{1-4} alkyl, p is 0, 1, or 2. Z represents halogen, C_{1-4} alkyl, or C_{1-4} alkoxy; and q is 0, 1, or 2. L represents a chemical bond; C_{1-4} alkylene; O; O(C_{1-4} alkylene); CII(C_{1-6} alkoxy); $S(O)_{0-2}$; $S(O)_{0-2}$(C_{1-4} alkylene); (C_{1-4} alkylene)$S(O)_{0-2}$; $NH(C_{1-4}$ alkylene); C(O); or C(O)-(C_{1-4} alkylene). D represents pyridinyl; imidazolyl; thiazolyl; pyrrolyl; thienyl; pyrazolyl; furyl; thiadiazolyl; oxazolyl; or benzimidazolyl. The pyridinyl and benzimidazolyl groups D each may be optionally substituted by up to three substituents independently selected from C_{1-4} alkyl, OH, C_{1-4} alkoxy, CN, NR^1R^2, $C(O)NR^1R^2$, halogen, and $CO_2(C_{1-6}$ alkyl), in which R^1 and R^2 are independently selected from H, C_{1-4} alkyl, and C_{3-6} cycloalkyl. Alternatively, R^1 and R^2 may be joined to form a 5-6 membered saturated heterocycle (II) in which Q represents O, $S(O)_{0-2}$, N-Y^1, or $C(Y^1)_2$, pharmaceutical compositions containing them, a method of making them, and methods of using them for treatment of cell proliferative diseases such as cancer, and non-malignant cell proliferative diseases, as well as osteoporosis and inflammatory diseases.

WO 03/026664 A1

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

APPLICATION FOR PATENT

2-PHENYLAMINO-4-(5-PYRAZOLYLAMINO)-PYRIMIDINE DERIVATIVES AS KINASE INHIBITORS, IN PARTICULAR, SRC KINASE INHIBITORS

Field of the Invention

The present invention relates to substituted pyrimidine compounds, and in particular, 2,4-diamine-substituted pyrimidine compounds, and pharmaceutical compositions thereof, and the use of such substituted pyrimidine compounds as inhibitors of src kinase enzymes.

Background of the Invention

Normal tissue homeostasis is achieved by an intricate balance between the rate of cell proliferation and cell death. Disruption of this balance, e.g., by increasing the rate of cell proliferation, modulating the rate of cell differentiation or decreasing the rate of cell death, can result in the abnormal growth of cells and is thought to be a major event in the development of cancer, as well as other cell proliferative disorders such as restenosis.

Proliferative disorders, e.g., cancer, causes significant numbers of deaths. For example, cancer causes over half a million deaths per year in the United States alone. Conventional strategies for the treatment of cancer include chemotherapy, radiotherapy, surgery or combinations thereof, however further advances in these strategies are limited by lack of specificity and excessive toxicity to normal tissues. In addition, certain cancers are refractory to treatments such as chemotherapy, and some of these strategies such as surgery are not always viable alternatives. For example, non-small-cell lung cancer (NSCLC), which includes squamous cell carcinoma, adenocarcinoma and large-cell carcinoma, accounts for 75-80% of all lung cancers (American Cancer Society, 1993). Current multimodality therapeutic strategies applied to regionally advanced NSCLC are minimally effective with the overall cure rate being only about 10% (Belani (1993) Semin Oncol. 20:302 and Roth *et al.* (1994) Lung Cancer 11 Suppl 3:S25).

Cell growth, differentiation and other cell processes are regulated by signal transduction pathways involving protein phosphorylation. Protein phosphorylation is the result of the transfer of a terminal phosphate of adenosine triphosphate to a particular amino

acid of a protein. This transfer is catalyzed by enzymes termed kinases. Protein kinases comprise a large superfamily of homologous proteins. They are related by their kinase or catalytic domains, which consists of approximately 250-300 amino acid residues. There are two main categories within the superfamily of protein kinases: the protein-serine/threonine kinses and the protein-tyrosine kinases (Hanks *et al.*, (1995) FASEB J. 9:576)

Kinases having an abnormal activity, e.g., mutated kinases, or abnormal levels of kinases, have been associated with abnormal cellular processes, which result in specific diseases. For example, several oncogenes, which are capable of transforming cells, are mutated forms of normal genes encoding kinases. Examples of such oncogenes include the pp60-v-src gene from the Rous avian sarcoma virus, which corresponds to the normal (i.e., proto-oncogene) gene pp60-c-src, containing a deletion that removes the C-terminal 18 amino acids of c-src. Pp60-c-src is also referred to as "src kinase" or "src tyrosine kinase." Phosphorylation of a tyrosine residue at position 527 of c-src protein causes a great reduction in its kinase activity, and this site is often altered in oncogenic derivatives of c-src (*see, e.g.,* Brown *et al.*, (1996) Biochem. Biophys. Acta 1287:121). Other proto-oncogenes encoding tyrosine kinases, which when mutated or over-expressed, cause cells to become transformed, include c-yes; c-fps (c-fes); c-abl and c-met. c-abl and c-met are associated with chronic myelogenous leukemia and osteosarcoma, respectively. Proto-oncogenes encoding serine/threonine kinases include c-mos and c-raf (c-mil). Whereas the above-cited proto-oncogenes are intracellular transducers, other proto-oncogenes encode kinases which are cell-surface receptors. Examples of proto-oncogenes encoding cell surface receptors with tyrosine kinase activity include c-fms (or Colony Stimulating Factor -1 (CSF-1) receptor); c-erbB, which is an epidermal growth factor receptor; c-neu (or erbB-2), erbB-3 or erbB-4 which are related to epidermal growth factor receptor; and c-ros, which is related to the insulin receptor.

The role of abnormal kinase activity or protein levels in diseases has been abundantly documented. This has been demonstrated, e.g., by using inhibitors of kinases, in particular tyrosine kinases. Such inhibitors have been shown to be useful for the treatment of disease states characterized by uncontrolled cell proliferation, e.g., cancer, inflammation, psoriasis, pulmonary fibrosis, glomerulonephritis, atherosclerosis, osteoporosis and restenosis following angioplasty. For example, tyrosine kinase inhibitors with selectivity for the EGF receptor family have been shown to block tumor formation in animals, thus demonstrating

their potential usefulness for directly suppressing tumor cell growth in the treatment of human cancer, especially breast carcinoma. Also, tumor metastasis and its associated angiogenesis has been shown to be inhibited by preventing the activation of the vascular endothelial growth factor receptor tyrosine kinase which indicates a utility for tyrosine kinase inhibitors in blocking separate events that occur during carcinogenesis. Thus, protein phosphorylation, e.g., tyrosine phosphorylation, plays an important role in cell regulatory processes, e.g., cell proliferation, and in diseases.

The pp60c-src protein has significant structural homology to about ten proteins (collectively referred to as Src Family kinases or SFKs) which include: Lck, Fyn, Yes, Yrk, Blk, Fgr, Hck, Lyn, and Frk subfamily members Frk/Rak and Iyk/Bsk (Sawyer *et al.*, (2001) Expert Opin. Investig. Drugs 10(7):1327). The Src family of tyrosine kinases, has three major domains: src homology SH1, SH2, and SH3 domains. The SH1 domain is most commonly called the catalytic domain or tyrosine kinase domain. The SH3 domain is a binding region for proteins having proline-rich sequences. Both the SH2 and SH3 domains are noncatalytic, but are important in protein-protein recognition. SH2 domains are homologous motifs of approximately 100 amino acids, which recognize and bind to the phosphorylated sequences present on regulatory proteins and growth factor receptors (Anderson *et al.*, *Science*, 1990, *250*, 979).

One of the primary purposes of the src family phosphoprotein/SH2 domain interaction is to initiate the association of proteins into an activation complex, often around the intracellular domain of the receptor itself. This role of the src family SH2 domain mediates and organizes the ordered, physical assembly of the various proteins in the activation complex. The activity of a number of immunologically important src family SH2 domain-containing proteins, including, Fyn, Fgr, Yes, Lyn, Hck and Lck, is mediated in this way. P56lck is of particular interest because it has been associated with the signal transduction cascade needed for T-cell activation mediated by the T-cell receptor (TCR) (Straus *et al.* (1992) *Cell*, *70*, 585).

The Src family of protein kinases, which all contain an SH2 domain, are involved in a number of cellular signalling pathways. For example, Src is involved in growth factor receptor signaling; integrin-mediated signaling; T- and B-cell activation; osteoclast activation; cell adhesion; cell motility and cell survival. It is known that the Src SH2 domain binds to several key receptor and nonreceptor tyrosine kinases such as tyrosine kinases

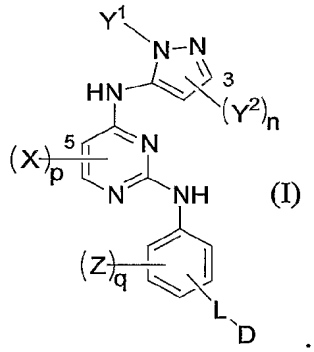
containing receptors for PDGF, EGF, HER2/Neu (an oncogene form of EGF), Fibroblast Growth Factor (FGF), focal adhesion kinase, p130 protein, and p68 protein. In addition, src has been shown to be involved in the regulation of DNA synthesis, mitosis, and other cellular activities (*see, e.g.,* Susa *et al.* (2000) Trends Pharm. Sciences 21:489).

Current cancer therapies utilize a battery of cytotoxic agents and radiation regimens to both decrease and eradicate tumors. The therapeutic index associated with these therapies is narrow and patients suffer from toxic side effects such as hair loss, bone marrow toxicity, loss of intestinal epithelium and mucositis. Many patients derive a therapeutic benefit from such treatment with an initial reduction in tumor mass and stabilization of the disease. However, recurrence is common and many times the tumors acquire a drug resistant phenotype and are refractory to future treatment with chemotherapeutic agents.

The need exists for kinase inhibitors, such as tyrosine kinase inhibitors, that overcome the above-mentioned deficiencies.

Summary of the Invention

In one embodiment, the invention provides compounds for regulating cellular processes involving a kinase such as a tyrosine kinase, in particular, a src kinase. In its broad aspect the invention relates to a compound of the formula (I)



In formula (I), the variables are as follows. Y^1 represents H or C_{1-4} alkyl. Y^2 represents CF^3; C_{1-6} alkyl; C_{3-6} cycloalkyl; or phenyl optionally substituted with halogen, C_{1-4} alkyl, or C_{1-4} alkoxy. The subscript n is 0, 1, or 2.

X represents halogen or C_{1-4} alkyl, and p is 0, 1, or 2.

Z represents halogen, C_{1-4} alkyl, or C_{1-4} alkoxy; and q is 0, 1, or 2.

L represents a chemical bond; C_{1-4} alkylene; O; O(C_{1-4} alkylene); CH(C_{1-6} alkoxy); $S(O)_{0-2}$; $S(O)_{0-2}$(C_{1-4} alkylene); (C_{1-4} alkylene)$S(O)_{0-2}$; NH(C_{1-4} alkylene); C(O); or

$C(O)$-(C_{1-4} alkylene).

D represents pyridinyl; imidazolyl; thiazolyl; pyrrolyl; thienyl; pyrazolyl; furyl; thiadiazolyl; oxazolyl; or benzimidazolyl. The pyridinyl and benzimidazolyl groups D each may be optionally substituted by up to three substituents independently selected from C_{1-4} alkyl, OH, C_{1-4} alkoxy, CN, NR^1R^2, $C(O)NR^1R^2$, halogen, and $CO_2(C_{1-6}$ alkyl), in which R^1 and R^2 are independently selected from H, C_{1-4} alkyl, and C_{3-6} cycloalkyl. Alternatively, R^1 and R^2 may be joined to form a 5-6 membered saturated heterocycle

in which Q represents O, $S(O)_{0-2}$, N-Y^1, or $C(Y^1)_2$. A pharmaceutically acceptable salt of this material is also within the scope of the invention. Examples of "5-6 membered saturated heterocycles" include, but are not limited to, morpholinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, or piperazinyl.

In another aspect, the invention relates to a pharmaceutical composition comprising a compound of formula (I) as described above, and a pharmaceutically acceptable carrier.

In yet another embodiment, the invention provides methods for regulating cellular processes involving a kinase such as a tyrosine kinase. In a preferred embodiment, the cellular process involves a src kinase. The cellular process can be, e.g., cell proliferation or cell differentiation.

The invention provides methods for treating diseases associated with a kinase, e.g., diseases associated with an abnormal kinase activity or level, such as cancers, osteoporosis, and inflammatory disorders. The invention also provides methods for treating diseases associated with abnormal cell proliferation and/or differentiation. In a preferred embodiment, the method comprises administering to a subject in need thereof, a pharmaceutically efficient amount of a compound of the invention, such that the subject is treated.

The invention also provides methods for preparing the compounds of the present invention. Also within the scope of the invention are kits comprising one or more compounds of the invention, optionally in a pharmaceutical composition.

Detailed Description of the Invention

The invention is based at least in part on the observation that 2,4-diamino substituted pyrimidine compounds inhibit the activity of src kinases. Exemplary compounds are described herein.

In formula (I), Y^1 preferably represents H. Preferably, Y^2 represents CF^3; C_{1-6} alkyl; C_{3-6} cycloalkyl; or phenyl optionally substituted with halogen, C_{1-4} alkyl, or C_{1-4} alkoxy; and n is 1 or 2. More preferably, Y^2 represents C_{1-6} alkyl; C_{3-6} cycloalkyl; or phenyl optionally substituted with halogen, C_{1-4} alkyl, or C_{1-4} alkoxy. Most preferably, Y^2 represents C_{1-6} alkyl or C_{3-6} cycloalkyl.

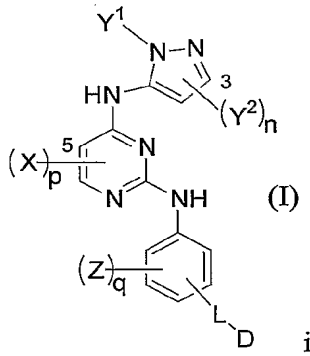
X preferably represents Cl, F, or C_{1-4} alkyl; and p is 0 or 1. More preferably, X represents F or C_{1-4} alkyl. Most preferably, X represents F.

Z preferably represents Cl, F, C_{1-4} alkyl, or C_{1-4} alkoxy; and q is 0 1, or 2. More preferably, Z represents F, C_{1-4} alkyl, or C_{1-4} alkoxy; and q is 0 or 1. Most preferably, Z represents C_{1-4} alkyl, or C_{1-4} alkoxy.

L preferably represents a chemical bond; C_{1-4} alkylene; $O(C_{1-4}$ alkylene); $CH(C_{1-6}$ alkoxy); $S(O)_{0-2}(C_{1-4}$ alkylene); $(C_{1-4}$ alkylene$)S(O)_{0-2}$; $NH(C_{1-4}$ alkylene); or $C(O)$-$(C_{1-4}$ alkylene). More preferably, L represents a chemical bond; C_{1-4} alkylene; $O(C_{1-4}$ alkylene); $S(O)_{0-2}(C_{1-4}$ alkylene); $(C_{1-4}$ alkylene$)S(O)_{0-2}$, or $NH(C_{1-4}$ alkylene). Most preferably, L represents C_{1-4} alkylene; $O(C_{1-4}$ alkylene); or $NH(C_{1-4}$ alkylene).

D preferably represents pyridinyl; imidazolyl; thiazolyl; pyrrolyl; pyrazolyl; or benzimidazolyl. The substituent groups on the pyridinyl and benzimidazolyl moieties are as described above. More preferably, D represents pyridinyl; imidazolyl; thiazolyl; pyrrolyl; or pyrazolyl. Most preferably, D represents pyridinyl or imidazolyl.

In a preferred embodiment, the compounds of the invention have the formula (I)



(I)

in which

Y^1 represents H or C_{1-4} alkyl. Y^2 represents CF^3; C_{1-6} alkyl; C_{3-6} cycloalkyl; or phenyl optionally substituted with halogen, C_{1-4} alkyl, or C_{1-4} alkoxy; and n is 1 or 2.

X represents Cl, F, or C_{1-4} alkyl; and p is 0 or 1.

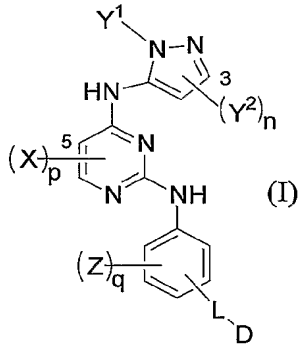
Z represents Cl, F, C_{1-4} alkyl, or C_{1-4} alkoxy; and q is 0 1, or 2.

L represents a chemical bond; C_{1-4} alkylene; $O(C_{1-4}$ alkylene); $CH(C_{1-6}$ alkoxy); $S(O)_{0-2}(C_{1-4}$ alkylene); $(C_{1-4}$ alkylene$)S(O)_{0-2}$; $NH(C_{1-4}$ alkylene); or $C(O)$-$(C_{1-4}$ alkylene).

D represents pyridinyl; imidazolyl; thiazolyl; pyrrolyl; pyrazolyl; or benzimidazolyl. These pyridinyl and benzimidazolyl groups D each may be optionally substituted by up to three substituents independently selected from C_{1-4} alkyl, OH, C_{1-4} alkoxy, CN, NR^1R^2, $C(O)NR^1R^2$, halogen, and $CO_2(C_{1-6}$ alkyl). In these substituents, R^1 and R^2 are independently selected from H, C_{1-4} alkyl, and C_{3-6} cycloalkyl, or alternatively, R^1 and R^2 may be joined to form a 5-6 membered saturated heterocycle

in which Q represents O, $S(O)_{0-2}$, N-Y^1, or $C(Y^1)_2$.

In a more preferred embodiment, the compounds of the invention have formula (I)



(I)

in which

Y^1 represents H. Y^2 represents C_{1-6} alkyl, C_{3-6} cycloalkyl, or phenyl optionally

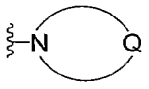
substituted with halogen, C_{1-4} alkyl, or C_{1-4} alkoxy; and n is 1 or 2.

X represents F or C_{1-4} alkyl; and p is 0 or 1.

Z represents F, C_{1-4} alkyl, or C_{1-4} alkoxy; and q is 0 or 1.

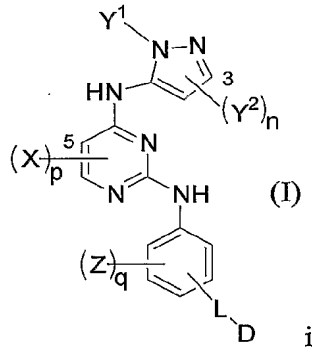
L represents a chemical bond; C_{1-4} alkylene; $O(C_{1-4}$ alkylene); $S(O)_{0-2}(C_{1-4}$ alkylene); $(C_{1-4}$ alkylene$)S(O)_{0-2}$, or $NH(C_{1-4}$ alkylene).

D represents pyridinyl; imidazolyl; thiazolyl; pyrrolyl; or pyrazolyl. The pyridinyl groups D each may be optionally substituted by up to three substituents independently selected from C_{1-4} alkyl, OH, C_{1-4} alkoxy, CN, NR^1R^2, $C(O)NR^1R^2$, halogen, and $CO_2(C_{1-6}$ alkyl). In these substituents, R^1 and R^2 are independently selected from H, C_{1-4} alkyl, and C_{3-6} cycloalkyl, or alternatively, R^1 and R^2 may be joined to form a 5-6 membered saturated heterocycle



wherein Q represents O, $S(O)_{0-2}$, N-Y^1, or $C(Y^1)_2$.

In a most preferred embodiment, the compounds of the invention have formula (I)



(I)

in which

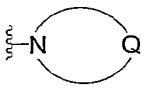
Y^1 represents H. Y^2 represents C_{1-6} alkyl or C_{3-6} cycloalkyl; and n is 1 or 2.

X represents F; and p is 0 or 1.

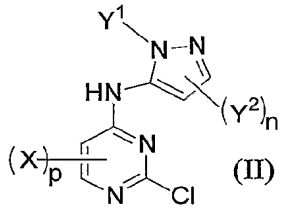
Z represents C_{1-4} alkyl or C_{1-4} alkoxy; and q is 0 or 1.

L represents C_{1-4} alkylene, $O(C_{1-4}$ alkylene), or $NH(C_{1-4}$ alkylene).

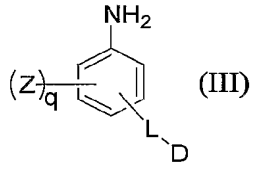
D represents pyridinyl or imidazolyl, and the pyridinyl groups D each may be optionally substituted by up to three substituents independently selected from C_{1-4} alkyl, OH, C_{1-4} alkoxy, CN, NR^1R^2, $C(O)NR^1R^2$, halogen, and $CO_2(C_{1-6}$ alkyl). In these substituents, R^1 and R^2 are independently selected from H, C_{1-4} alkyl, and C_{3-6} cycloalkyl, or alternatively, R^1 and R^2 may be joined to form a 5-6 membered saturated heterocycle


in which Q represents O, $S(O)_{0-2}$, N-Y^1, or $C(Y^1)_2$.

The compounds of formula (I) are generally made by coupling a compound of formula (II)

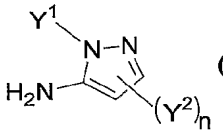

(II)

with a compound of formula (III)

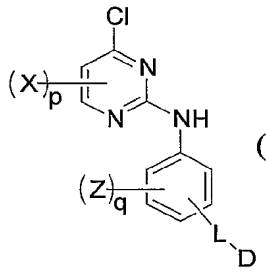

(III)

or

coupling a compound of formula (IV)


(IV)

with a compound of formula (V)


(V)

, to yield a compound of formula (I). In formulae (II), (III), (IV), and (V), the meanings of the substituent groups are as described above.

In Formula (I), X is preferably in the 5-position of the pyrimidine ring, Y^2 is preferably in the 3-position of the pyrazole ring, and L-D is preferably *meta* or *para* to the amino N.

Definitions

For convenience, certain terms employed in the specification, examples, and appended claims are collected here.

The terms "a" and "an" refer to "one or more" when used in this application, including the claims.

"Abnormal growth of cells" means cell growth independent of normal regulatory mechanisms (e.g., loss of contact inhibition).

The term "analog" of a compound refers to a compound having structural similarity to a particular compound and having essentially the same type of biological activity as the compound.

The term "antiproliferative" therapeutic or compound refers to a compound or therapeutic which inhibits cell proliferation to at least some extent.

The term "cytostatic" when referring to the activity of a compound means that the compound causes the cell to cell cycle arrest, but it does not kill the cell. Thus, removal of the drug from the environment of the cell results in the resumption of cell proliferation.

The term "derivative" of a compound or of a small molecule refers to a compound which can be derived, e.g., by chemical synthesis, from the original compound. Thus a derivative of a compound has certain structural similarities with the compound.

"Disease associated with an abnormal activity or level of a kinase" refers to a disease in which an abnormal activity or protein level of a kinase is present in certain cells, and in which the abnormal activity or protein level of the kinase is at least partly responsible for the disease.

A "disease associated with a kinase" refers to a disease that can be treated with a kinase inhibitor.

"Diseases associated with src kinase-mediated signaling" refers to diseases which can be treated with an inhibitor of src kinase-mediated signaling. Such disease can, e.g., be associated with an abnormal src kinase activity or level.

The terms "excessive cell proliferation," used interchangeably herein with "hyper-proliferation" of cells refers to cells which divide more often than their normal or wild-type counterpart. Thus, cells are excessively proliferating when they double in less than 24 hours if their normal counterparts double in 24 hours. Excessive proliferation can be detected by simple counting of the cells, with or without specific dyes, or by detecting DNA replication

or transcription, such as by measuring incorporation of a labeled molecule or atom into DNA or RNA.

"Inhibiting cell proliferation" refers to decreasing the rate of cell division, by interrupting or slowing down the cell cycle. The term refers to complete blockage of cell proliferation, i.e., cell cycle arrest, as well as to a lengthening of the cell cycle. For example, the period of a cell cycle can be increased by about 10%, about 20%, about 30, 40, 50, or 100%. The duration of the cell cycle can also be augmented by a factor of two, three, 4, 5, 10 or more.

"Modulating cell differentiation" refers to the stimulation or inhibition of cell differentiation.

"Normalizing cell proliferation" refers to reducing the rate of cell proliferation of a cell that proliferates excessively relative to that of its normal or wild-type counterpart, or increasing the rate of cell proliferation of a cell that proliferates poorly relative to its normal or wild-type counterpart.

A "patient" or "subject" to be treated by the subject method can mean either a human or non-human animal.

The term "proliferative disorder" refers to any disease/disorder of a tissue marked by unwanted or aberrant proliferation of at least some cells in the tissue. Such diseases include cancer, as well as benign diseases or disorders, such as warts or other benign tumors.

A "src inhibitor" is a compound which inhibits at least part of the activity of a src kinase in a cell. The inhibition can be, at least about 20%, preferably at least about 40%, even more preferably at least about 50%, 70%, 80%, 90%, 95%, and most preferably at least about 98% of the activity of the src kinase.

"Treating" a disease refers to preventing, curing or improving at least one symptom of a disease.

The following definitions pertain to the structure of the compounds:

The abbreviations Me, Et, and Ph, represent methyl, ethyl, and phenyl, respectively. A more comprehensive list of the abbreviations utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the *Journal of Organic Chemistry* (i.e. *J. Org. Chem.* **1995**, *60*, 12a.). This list is typically presented in a table entitled Standard List of Abbreviations. The abbreviations contained in this list are hereby incorporated by reference.

"Alkyl" means a hydrocarbon radical having up to a maximum of 12 carbon atoms, which may be linear or branched with single or multiple branching. Alkyl is especially lower alkyl. Examples of such alkyl groups are methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, and isohexyl.

"Halogen" means fluorine, chlorine, bromine, or iodine but is especially fluorine, chlorine, or bromine.

"Cycloalkyl" is a saturated carbocycle that contains between 3 and 12 carbons but preferably 3 to 8 carbons. Examples include the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl groups.

The term "alkoxy" means a group in which the alkyl portion is straight or branched and has the designated number of carbon atoms. Examples of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, and isohexoxy.

The term "optionally" means that the subsequent desribed event(s) may or may not occur, and includes both event(s), which occur, and event(s) that do not occur.

Abbreviations and Acronyms

When the following abbreviations are used throughout the disclosure, they have the follow meaning:

AcOH	acetic acid
AgOTf	silver trimethanesulfonate
ATP	adenosine triphosphate
Ar	argon
BH_3·THF	borane-tetrahydrofuran complex
BOC	*tert*-Butoxycarbonyl
BRIJ	polyoxyethylene(23) lauryl ether
BSA	bovine serum albumin
n-BuLi	butyllithium
n-BuOH	1-butanol
CBr_4	carbontetrabromide
CD_3OD	methanol-d_4

$CDCl_3$	chloroform-*d*
$CHCl_3$	chloroform
CH_2Cl_2	methylene chloride
CH_3CN	acetonitrile
Cs_2CO_3	cesium carbonate
DCE	1,2-dichloroethane
dH_2O	de-ionized water
DMAP	4-dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	dimethylsulfoxide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ESI-MS	electrospray ionization mass spectrometry
EDTA	ethylenediaminetetraacetic acid
Et_3N	triethylamine
EtOAc	ethyl acetate
Et_2O	diethyl ether
EtOH	ethanol
$FeSO_4$	iron (II) sulfate
H_2	hydrogen gas
HCl	hydrochloric acid
H_2O_2	hydrogenperoxide
HEPES	4-(2-hydroxyethyl)-1-piperazineethane-sulfonic acid
HEX	hexanes
^1H NMR	proton nuclear magnetic resonance
H_2SO_4	sulfuric acid
HPLC	high performance liquid chromatography
K_2CO_3	potassium carbonate
KNO_3	potassium nitrate
KOAc	potassium acetate
KOH	potassium hydroxide
LC/MS	liquid chromatography / mass spectroscopy
MCPBA	3-chloroperoxybenzoic acid

MeOH	methanol
$MgSO_4$	anhydrous magnesium sulfate
MMTV	murine mammary tumor virus
MnO_2	manganese (II) oxide
MS ES	mass spectroscopy with electrospray
$NaBH_4$	sodium borohydride
$NaCNBH_3$	sodium cyanoborohydride
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
NaI	sodium iodide
NaOH	sodium hydroxide
Na_2SO_4	sodium sulfate
NH_3	ammonia
NH_4Cl	ammonium chloride
NH_4OH	ammonium hydroxide
NMM	*N*-methylmorpholine
Pd/C	palladium on carbon
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
P_2O_5	phosphorus pentoxide
Poly-GAT	poly glycine, alanine, tyrosine
PPh_3	triphenylphosphine
PS-NCO	polystyrene isocyanate
RNA	ribonucleic acid
$SnCl_2$	tin (II) chloride
Streptavidin-APC	steptavadin conjugated allopycocyanin
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMSCl	chlorotrimethylsilane
TMSCN	trimethylsilyl cyanide
TLC	thin layer chromatography

Compounds of the Invention

The present invention provides substituted pyrimidine compounds, e.g., 2,4-diamino substituted pyrimidine compounds, which are capable of inhibiting src kinase activity. Preferred compounds of the invention have the IUPAC names set forth below:

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Example #	IUPAC NAME
1	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-[4-(3-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
2	N^2-{4-[butoxy(3-pyridinyl)methyl]phenyl}-N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-2,4-pyrimidinediamine
3	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-{3-[(4-methyl-3-pyridinyl)methyl]phenyl}-2,4-pyrimidinediamine
4	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-{3-[(4-methyl-3-pyridinyl)methyl]phenyl}-2,4-pyrimidinediamine
5	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-(4-{[6-(4-morpholinyl)-3-pyridinyl]methyl}phenyl)-2,4-pyrimidinediamine
6	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-(4-{[6-(methylamino)-3-pyridinyl]methyl}phenyl)-2,4-pyrimidinediamine
7	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-[3-(1*H*-pyrazol-3-yl)phenyl]-2,4-pyrimidinediamine
8	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-[3-(1,3-thiazol-5-ylmethyl)phenyl]-2,4-pyrimidinediamine
9	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-[4-(1,2,3-thiadiazol-4-yl)phenyl]-2,4-pyrimidinediamine

10	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-{3-[2-(4-pyridinyl)ethyl]phenyl}-2,4-pyrimidinediamine
11	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-{3-[2-(4-pyridinyl)ethyl]phenyl}-2,4-pyrimidinediamine
12	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-{4-[(4-pyridinylsulfanyl)methyl]phenyl}-2,4-pyrimidinediamine
13	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-{4-[(4-pyridinylmethyl)sulfanyl]phenyl}-2,4-pyrimidinediamine
14	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-{4-[(4-pyridinylmethyl)sulfanyl]phenyl}-2,4-pyrimidinediamine
15	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-[3-(4-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
16	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-[3-(4-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
17	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-[4-(3-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
18	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-{3-[(2-pyridinylmethyl)amino]phenyl}-2,4-pyrimidinediamine
19	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-{3-[(2-pyridinylmethyl)amino]phenyl}-2,4-pyrimidinediamine
20	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-{3-[(3-pyridinylmethyl)amino]phenyl}-2,4-pyrimidinediamine
21	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-{3-[(3-pyridinylmethyl)amino]phenyl}-2,4-pyrimidinediamine
22	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-{3-[(4-pyridinylmethyl)amino]phenyl}-2,4-pyrimidinediamine
23	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-{3-[(4-pyridinylmethyl)amino]phenyl}-2,4-pyrimidinediamine
24	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-(3-{[(2-methyl-1*H*-imidazol-4-yl)methyl]amino}phenyl)-2,4-

	pyrimidinediamine
25	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-(3-{[(2-methyl-1*H*-imidazol-4-yl)methyl]amino}phenyl)-2,4-pyrimidinediamine
26	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-{3-[(1*H*-imidazol-2-ylmethyl)amino]phenyl}-2,4-pyrimidinediamine
27	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-{3-[(1*H*-imidazol-2-ylmethyl)amino] phenyl}-2,4-pyrimidinediamine
28	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-{3-[2-(2-pyridinyl)ethyl]phenyl}-2,4-pyrimidinediamine
29	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-{3-[2-(2-pyridinyl)ethyl]phenyl}-2,4-pyrimidinediamine
30	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-{3-[(3-furylmethyl)amino]phenyl}-2,4-pyrimidinediamine
31	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-{3-[(3-thienylmethyl)amino]phenyl}-2,4-pyrimidinediamine
32	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-(3-{[(1-methyl-1*H*-pyrrol-2-yl)methyl]amino}phenyl)-2,4-pyrimidinediamine
33	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-{3-[(1,3-thiazol-2-ylmethyl)amino]phenyl}-2,4-pyrimidinediamine
34	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-{3-[2-(3-pyridinyl)ethyl]phenyl}-2,4-pyrimidinediamine
35	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-{3-[2-(3-pyridinyl)ethyl]phenyl}-2,4-pyrimidinediamine
36	3-[4-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-2-pyrimidinyl}amino)phenoxy]-*N*-methylbenzamide
37	[3-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-2-pyrimidinyl}amino)phenyl](4-pyridinyl)methanone
38	[3-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-2-pyrimidinyl}amino)phenyl](3-pyridinyl)methanone

39	[3-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-5-fluoro-2-pyrimidinyl}amino)phenyl](3-pyridinyl)methanone
40	[3-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-2-pyrimidinyl}amino)phenyl](2-pyridinyl)methanone
41	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-[3-(3-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
42	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-[3-(3-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
43	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-[3-(4-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
44	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-[3-(4-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
45	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-[3-(2-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
46	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-[3-(2-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
47	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-[4-methoxy-3-(3-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
48	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-[4-methoxy-3-(2-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
49	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-[4-methoxy-3-(2-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
50	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-[4-methoxy-3-(3-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
51	1-[5-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-2-pyrimidinyl}amino)-2-methoxyphenyl]-2-(1*H*-imidazol-1-yl)ethanone
52	1-[5-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-2-pyrimidinyl}amino)-2-methylphenyl]-2-(1*H*-imidazol-1-yl)ethanone

53	1-[5-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-5-fluoro-2-pyrimidinyl}amino)-2-methylphenyl]-2-(1*H*-imidazol-1-yl)ethanone
54	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-(3-{[2-(1*H*-imidazol-1-yl)ethyl]amino}phenyl)-2,4-pyrimidinediamine
55	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-[3-(1*H*-imidazol-1-ylmethyl)phenyl]-2,4-pyrimidinediamine
56	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro- N^2-[3-(1*H*-imidazol-1-ylmethyl)phenyl]-2,4-pyrimidinediamine
57	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-[3-(1*H*-imidazol-1-ylmethyl)-4-methoxyphenyl]-2,4-pyrimidinediamine
58	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro- N^2-[3-(1*H*-imidazol-1-ylmethyl)-4-methoxyphenyl]-2,4-pyrimidinediamine
59	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-[4-(1*H*-imidazol-1-ylmethyl)phenyl]-2,4-pyrimidinediamine
60	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro- N^2-[4-(1*H*-imidazol-1-ylmethyl)phenyl]-2,4-pyrimidinediamine
61	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-[3-(3-pyridinylsulfanyl)phenyl]-2,4-pyrimidinediamine
62	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-{3-[2-(1H-pyrazol-1-yl)ethoxy]phenyl}-2,4-pyrimidinediamine
63	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-{4-chloro-3-[2-(1*H*-pyrazol-1-yl)ethoxy]phenyl}-2,4-pyrimidinediamine
64	1-{2-[3-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-2-pyrimidinyl}amino)phenoxy]ethyl}-1*H*-benzimidazole-5-carboxylic acid
65	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-[3-(1,3-oxazol-5-yl)phenyl]-2,4-pyrimidinediamine
66	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-[3-(3-pyridinyloxy)phenyl]-2,4-pyrimidinediamine

67	[3-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-2-pyrimidinyl}amino)phenyl](6-methoxy-3-pyridinyl)methanone
68	5-bromo-N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-[4-(3-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
69	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-methyl-N^2-[4-(3-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
70	5-[4-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-2-pyrimidinyl}amino)benzyl]-2-pyridinol
71	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-{4-[(6-fluoro-3-pyridinyl)methyl]phenyl}-2,4-pyrimidinediamine
72	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-{4-[(6-fluoro-3-pyridinyl)methyl]phenyl}-2,4-pyrimidinediamine
73	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-{3-[3-(1*H*-imidazol-1-yl)propyl]phenyl}-2,4-pyrimidinediamine
74	N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-{3-[3-(1*H*-imidazol-1-yl)propyl]phenyl}-2,4-pyrimidinediamine
75	N^4-(3-tert-butyl-1*H*-pyrazol-5-yl)- N^2-{3-[2-(1*H*-imidazol-1-yl)ethoxy]phenyl}-2,4-pyrimidinediamine
76	N^4-(3-tert-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-{3-[2-(1*H*-imidazol-1-yl)ethoxy]phenyl}-2,4-pyrimidinediamine
77	N^4-(3-tert-butyl-1*H*-pyrazol-5-yl)- N^2-{3-[2-(1*H*-imidazol-1-yl)ethoxy]phenyl}-5-methyl-2,4-pyrimidinediamine
78	N^4-(3-tert-butyl-1*H*-pyrazol-5-yl)- N^2-{3-[2-(1*H*-imidazol-1-yl)ethoxy]-4-methoxyphenyl}-2,4-pyrimidinediamine
79	N^4-(3-tert-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-{3-[2-(1*H*-imidazol-1-yl)ethoxy]-4-methoxyphenyl}-2,4-pyrimidinediamine
80	N^4-(3-tert-butyl-1*H*-pyrazol-5-yl)- N^2-{3-[2-(1*H*-imidazol-1-yl)ethoxy]-4-methylphenyl}-2,4-pyrimidinediamine

81	N^4-(3-tert-butyl-1*H*-pyrazol-5-yl)-5-fluoro-N^2-{3-[2-(1*H*-imidazol-1-yl)ethoxy]-4-methylphenyl}-2,4-pyrimidinediamine
82	3-[4-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-2-pyrimidinyl}amino)benzyl]-2-pyridinecarbonitrile
83	3-[4-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-5-fluoro-2-pyrimidinyl}amino)benzyl]-2-pyridinecarbonitrile
84	3-[4-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-5-fluoro-2-pyrimidinyl}amino)benzyl]-N-methyl-2-pyridinecarboxamide
85	N^4-(3-tert-butyl-1*H*-pyrazol-5-yl)-N^2-(4-{[2-(4-morpholinylcarbonyl)-3-pyridynl]methyl}phenyl)-2,4-pyrimidinediamine
86	butyl 3-[4-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-2-pyrimidinyl}amino)benzyl]-2-pyridinecarboxylate
87	butyl 4-[4-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-2-pyrimidinyl}amino)benzyl]-2-pyridinecarboxylate
88	4-[4-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-2-pyrimidinyl}amino)benzyl]-2-pyridinecarbonitrile
89	4-[4-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-5-fluoro-2-pyrimidinyl}amino)benzyl]-2-pyridinecarbonitrile hydrochloride
90	N^4-(3-tert-butyl-1*H*-pyrazol-5-yl)- N^2-{2-chloro-5-[2-(1*H*-imidazol-1-yl)ethoxy]phenyl}-2,4-pyrimidinediamine
91	N^4-(3-methyl-1*H*-pyrazol-5-yl)-N^2-[4-(3-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
92	N^4-[3-(4-chlorophenyl)-1*H*-pyrazol-5-yl]-N^2-[4-(3-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
93	N^4-(3-*tert*-butyl-1-methyl-1*H*-pyrazol-5-yl)-N^2-[4-(3-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
94	N^4-(3-*tert*-pentyl-1*H*-pyrazol-5-yl)-N^2-[4-(3-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine

95	N^4-[3-(1-ethyl-1-methylpropyl)-1*H*-pyrazol-5-yl]-N^2-[4-(3-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
96	N^4-(3-cyclopropyl-1*H*-pyrazol-5-yl)-N^2-[4-(3-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
97	N^2-[4-(3-pyridinylmethyl)phenyl]-N^4-[3-(trifluoromethyl)-1*H*-pyrazol-5-yl]-2,4-pyrimidinediamine
98	N^4-(3-cyclopentyl-1*H*-pyrazol-5-yl)-N^2-[4-(3-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
99	N^4-(3-neopentyl-1H-pyrazol-5-yl)-N^2-[4-(3-pyridinylmethyl)phenyl]-2,4-pyrimidinediamine
100	3-[4-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-2-pyrimidinyl}amino)benzyl]-*N*-methylisonicotinamide
101	5-[4-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-2-pyrimidinyl}amino)benzyl]-*N*-methyl-2-pyridinecarboxamide

Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivatization with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group such as amino, or an acidic functional group such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

Contemplated equivalents of the compounds described above include compounds

which otherwise correspond thereto, and which have the same general properties thereof (e.g., functioning as src kinase inhibitors), wherein one or more simple variations of substituents are made which do not adversely affect the efficacy of the compound in inhibiting src kinases.

In general, the compounds of the present invention may be prepared by the methods known to those skilled in the art as illustrated in the general reaction schemes as described below, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are in themselves known, but are not mentioned here.

Methods of use of the compounds of the invention

The compounds of the invention, including substituted pyrimidine compounds, salts, prodrugs, and compositions thereof, can be used for treating a disease or condition (generally referred to herein as " disease") associated with a kinase, such as a disease associated with an abnormal activity or level of a kinase. In a preferred embodiment, the kinase is a tyrosine kinase, such as a src tyrosine kinase. Generally, the compounds of the invention can be used for treating diseases that are associated with a component of the signal transduction pathway in which a kinase is involved. For example, it is expected that a cell proliferative disease resulting from over-expression of a signal transduction molecule or cell surface receptor that is in the same signal transduction pathway as that in which a kinase which can be inhibited by a compound of the invention is present, can also be treated with the compounds of the invention. At least for this reason, the compounds of the invention are expected to be effective against a broad range of target cells, and not only target cells having an abnormal activity or level of a kinase. The terms "target cell" refers to a cell towards which a compound is targeted. Furthermore, at least some of the compounds of the invention may also be effective against cells which proliferate and/or differentiate normally, i.e., wild-type cells. For example, certain compounds could be used to arrest cell proliferation, even if the cell proliferation is not abnormal.

In a preferred embodiment, the compounds of the invention are useful for treating a disease associated with a src kinase. Src kinases are involved in various cellular functions, including cell proliferation and transformation; cell adhesion, migration and chemotaxis; intracellular trafficking; and cell survival. Accordingly, diseases that can be treated

according to the invention include those which are dysfunctional in any of these cellular functions. Exemplary diseases are provided below.

In one embodiment, a therapeutic method comprises administering to a subject having a disease associated with a kinase, a pharmaceutically effective amount of a compound of the invention, such that the disease is treated. The subject is preferably a mammal, e.g., a human, non-human primate, bovine, ovine, porcine, feline, canine, mouse or rat. The compounds can be administered via various routes depending on the disease to be treated. Methods of administration are further described herein. Non-mammalian cells, which share essentially the same signal transduction pathways as those in mammalian cells, e.g., yeast cells, can also be target cells of the invention.

Compounds of the invention may specifically inhibit the activity of a single kinase, e.g., src kinase, or they may inhibit the activity of more than one kinase or more than one type of kinase. Accordingly, a compound of the invention could be used for treating one or more diseases associated with one or more kinases.

The efficacy of the compounds of the invention against a broad range of target cells allows for broad applications for these compounds. The following are exemplary therapeutic applications for the compounds of the invention. These exemplary therapeutic applications focus first on diseases associated with src tyrosine kinase and then describe other diseases that may also be treated with the compounds of the invention.

Src tyrosine kinase has specifically been implicated in the development, growth, progression, and metastasis of a number of human cancers such as colon, breast, pancreas and brain (*see, e.g.,* Irby and Yeatman (2000) Oncogene 19:5636), and these cancers are expected to be treatable with the compounds of the invention. For example, a src kinase activity from 4-20 fold higher than normal has been found in mammary carcinomas (Irby and Yeatman, *supra*; Egan *et al.* (1999) Oncogene 18:1227 and Verbeek *et al.* (1996) J. Pathol. 180:383).

c-src has also frequently been implicated in the initiation and progression of human colon cancer and in resultant metastases (*see, e.g.,* Cartwright *et al.* (1994) J. Clin. Invest. 93:509; Talamonti *et al.* (1991) J. Clin. Invest. 91:53; and Termuhlen *et al.* (1993) J. Surg. Res. 54). Src is increased 5-8 fold in the majority of colon tumors. Elevated src activity is also present in pre-cancerous colon lesions, e.g., adenomatous polyps (Pena *et al.* (1995) Gastroenterol. 108:117).

Other cancers that can be treated include pancreatic cancer (Flossmann-Kast *et al.* (1998) Cancer Res. 8:3551); and Visser *et al.* (1996) Lab. Invest. 74:2), lung cancer (Mazurenko *et al.* (1992) Eur. J. Cancer 28:372), neural cancer (Bjelfman *et al.* (1990) Cancer Res. 50:6908); ovarian cancer (Wiener *et al.* (1999) Clin. Cancer Res. 5:2164); esophageal adenocarcinomas and Barrett's (Kumble *et al.* (1997) Gastroeneterology 112:348); gastic cancers (Takeshima *et al.* (1991) Jpn. J. Cancer Res. 82:1428); melanomas (Bjorge *et al.* (1996) Biochem. Cell Biol. 74:477) and Kaposi's sarcoma (Munshi *et al.* (2000) J. Immunol. 164:1169). Src probably also contributes to tumor growth in synergy with receptor tyrosine kinases, such as c-met and those of the ErbB family (Biscardi *et al.* (1999) Adv. Cancer Res. 76: 6). Accordingly, all of the above are exemplary cancers that can be treated with the compounds of the invention.

The compounds of the invention can also be used to treat diseases associated with defects in cell adhesion and motility, such as angiogenesis, inflammation and bone resorption. Src has been shown to play a role in signal transduction via cell-adhesion receptors (integrins). Src dependent cell migration is important for the function of many cell types, e.g., the motility of osteoclasts and metastasizing cells (Chellaiah *et al.* (2000) J. Biol. Chem. 275:11993 and Susa and Teri (2000) Drug News Perpect. 13:169). Src dependent cell migration may also be important for the recruitment of vascular smooth muscle cell precursors in response to PDGF produced by endothelial cells during blood vessel formation (Hirschi *et al.* (1998) J. Cell. Biol. 141:805).

Src kinase is also involved in endocytosis, e.g., transcytosis, such as that which occurs in osteoclasts (Nesbitt and Horton (1997) Science 276:266). Src assists endocytosis of certain growth factor receptors, e.g., EGF receptors (Wilde *et al.* (1999) Cell 96:677). Blood vessel hyperpermeability induced by vascular endothelial growth factor (VEGF) is also dependent on src (Eliceiri *et al.* (1999) Mol. Cell 4:915). Src has been shown to also be involved in cell survival (reviewed in Susa *et al.* (2000) Trends in Pharmacol. Sci. 21:489). Accordingly, diseases related to any of these exemplary src biological activities can be treated with the compounds of the invention.

A preferred use for the compounds of the invention is for the treatment of osteoporosis, which involves bone resorption. Osteoporosis is a widespread disease of low bone mass that particularly affects post-menopausal women (*see, e.g.,* Gowen *et al.* (2000) Emerging Drugs 5:1). The role of src in bone metabolism was first demonstrated in src-

deficient mice and has been confirmed using small molecular weight inhibitors in animal models of osteoporosis. Src-deficient mice have defective bone resorption, resulting in excessive bone mass and osteopetrosis (*see, e.g.,* Thomas and Brugge (1997) Annu. Rev. Cell. Dev. Biol., 13: 513). The role of src in bone resorption is well recognized. A src inhibitor has been shown to reduce bone resorption in an animal model of osteoporosis (Missbach *et al.* (1992) Bone 24:437). The disorder is believed to be caused by dysfunctions in osteoclasts and osteoblasts, as well as in osteoclast survival and osteoclast formation (reviewed in Susa *et al., supra*).

Other diseases that may also be treated according to the invention include other types of malignancies, e.g., cancers of the brain, genitourinary tract, prostate, skin, lymphatic system, rectum, stomach, larynx, ovary, bladder, and liver. More particularly, such cancers include histiocytic lymphoma, lung adenocarcinoma, pancreatic carcinoma, colo-rectal carcinoma, bladder cancers, head and neck cancers, acute and chronic leukemias, melanomas, neurological tumor, myeloid leukemias (for example, acute myelogenousleukemia), sarcomas, thyroid follicular cancer, and myelodysplastic syndrome.

The compounds of the invention can also be used for treating disease associated with abnormal activity and/or expression of members of a growth factor family or receptors thereof. For example, compounds of the invention are expected to be effective against diseases associated with a defect in a growth factor or receptor of the EGF receptor family, such as Neu-erb2-related genes. The compounds of the invention are believed to be effective against the following diseases. For example, amplification and/or over-expression of human erbB2 gene, has been shown to correlate with a poor prognosis in breast and ovarian cancers, in particular, carcinomas (*see, e.g.,* Slamon *et al.*, Science 235:177-82 (1987); Slamon *et al.*, Science 244:707-12 (1989)). Overexpression of erbB2 has also been correlated with other carcinomas including carcinomas of the stomach, endometrium, salivary gland, lung, kidney, colon and bladder. ErbB1 has been causally implicated in human malignancy, e.g., aggressive carcinomas of the breast, bladder, lung, and stomach. ErbB gene amplification or overexpression, or a combination of both, has also been demonstrated in squamous cell carcinomas and glioblastomas (Libermann, T. A., Nusbaum, H. R., Razon, N., Kris, R., Lax, I., Soreq, H., Whittle, N., Waterfield, M.D., Ullrich, A. & Schlessinger, J., 1985, Nature 313:144-147). Accordingly, the compounds of the invention are believed to be useful for treating these malignancies. ErbB3 has been found to be overexpressed in breast (Lemoine

et al., Br. J. Cancer 66:1116-21 (1992)), gastrointestinal (Poller *et al.*, J. Pathol. 168:275-80 (1992); Rajkumer *et al.*, J. Pathol. 170:271-78 (1993); Sanidas *et al.*, Int. J. Cancer 54:935-40 (1993)), and pancreatic cancers (Lemoine *et al.*, J. Pathol. 168:269-73 (1992), and Friess *et al.*, Clinical Cancer Research 1:1413-20 (1995)). Plowman *et al.* found that Increased erbB4 expression have been found to closely correlate with certain carcinomas of epithelial origin, including breast adenocarcinomas (Plowman *et al.*, PNAS 90:1746-50 (1993) and Plowman *et al.*, Nature 366:473-75 (1993)).

The hyper-proliferative disorders that can be treated by the disclosed substituted pyrimidine compounds, salts, prodrugs and compositions thereof include, but are not limited to solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include, but are not limited to lymphomas, sarcomas, and leukemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer.

Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallblader, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, and urethral cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma

(intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to laryngeal / hypopharyngeal / nasopharyngeal / oropharyngeal cancer, and lip and oral cavity cancer. Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma. Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in man, but also exist with a similar etiology in other mammals, and can be treated by pharmaceutical compositions of the present invention.

Other types of proliferative disorders that can be treated according to the invention include non malignant cell proliferative disorders, such as those associated with an abnormal production of, or response to a growth factor, e.g., platelet derived growth factor (PDGF), fibroblast derived growth factor (FGF), epidermal derived growth factor (EGF) and vascular endothelial growth factor (VEGF). Exemplary diseases include restinosis, glomerulonephritis, neurofibromatosis, glaucoma, psoriasis, rheumatoid arthritis, inflammatory bowel disease, and chemotherapy-induced alopecia and mucositis.

Restenosis following coronary angioplasty is one major unsolved problem of interventional cardiology. Of the nearly 400,000 angioplasties currently performed in the United States each year, 25-34% fail within the first five years, of which most occur during the first year, due to restenosis (Geschwind H.J. (1995) Interv. Cardiol. 8:756 and The Merck Manual of Diagnosis and Therapy, 16th Ed. (1992) Merck Res. Lab., p. 406. The process of restenosis involves the reocclusion of an atherosclerotic artery which in many cases is due to the proliferation of smooth muscle cells which is mediated by growth factors such as PDGF and FGF. In animal models of restenosis, antibodies which block the activation of PDGF or FGF receptor tyrosine kinase activity prevent smooth muscle cell proliferation and the formation of neointima. These studies indicate that tyrosine kinase inhibitors that block PDGF or FGF receptor function could have utility in treating human restenosis.

In experimental models of glomerulonephritis, a 20-fold increase in PDGFR expression is associated with mesangial cell proliferation. Neutralization of PDGF which prevents the activation of its tyrosine kinase receptor limits the amount of renal degeneration which normally occurs. These studies demonstrate that a tyrosine kinase inhibitor which blocks PDGFR could have potential for the treatment of human glomerulonephritis. Johnson *et al.* (1992) J. Exp. Med. 175:1413.

In another embodiment, the compounds of the invention are used for treating inflammatory diseases, e.g., rheumatoid arthritis (R.A.). Synovial tissues of RA patients express high levels of FGF and PDGF compared with synovial tissues of osteoarthritis patients, a non invasive joint disease (Sano *et al.*, J. Cell. Biol. 110:1417-1426, 1990). These data are consistent with the theory that PDGF and FGF play a role in generating an invasive tumor-like behavior in arthritic joints of RA synovial connective tissues (Sano *et al.*, J. Clin. Invest. 91:553-565 1993).

It is further expected that the compounds of the invention are useful for treating smooth muscle cell hyper-proliferation, at least in part since PDGF is considered to be a principal growth-regulatory molecule responsible for smooth muscle cell proliferation. One smooth muscle disorder is atherosclerosis, which is a disease characterized by focal thickening of the inner portion of the artery wall, predisposing an individual to myocardial infarction (heart attack), cerebral infarction (stroke), hypertension (high blood pressure) and gangrene of the extremities. In addition to consisting primarily of proliferated smooth muscle cells, lesions of atherosclerosis are surrounded by large amounts of lipid-laden macrophages, varying numbers of lymphocytes and large amounts of connective tissue. PDGF has been found in numerous cells in such lesions, and it is believed that PDGF plays a critical role in the atherosclerosis disease process. Other smooth muscle diseases include diabetic vascular pathologies.

Both FGF and VEGF are potent angiogenic factors that induce formation of new capillary blood vessels. Accordingly, the compounds of the invention may be useful in inhibiting vascularization, e.g., in tumors.

In addition, the instant compounds may also be useful in the treatment of certain viral infections, in particular in the treatment of hepatitis C or delta and related viruses (Glenn *et al.* Science, 256:1331-1333 (1992)). Numerous viruses also induce non cancerous cell

proliferation. Examples include papilloma viruses (HPV), which create skin lesions. Such viral infections may also be treatable with the compositions of the invention.

The compounds of the invention can also be used for treatment of hyperproliferative cutaneous diseases, e.g., keratosis and psoriasis.

Also within the scope of the invention are methods for inhibiting growth of non-mammalian cells, which have similar signal transduction pathways as those in mammalian cells. Exemplary cells include yeast cells. Accordingly, the compounds of the invention can be used as anti-fungal agents to treat fungal infections on animals, e.g., humans. The compounds can also be used for stopping fungus growth on objects, e.g., mold or mildew growth on shower curtains.

A person of skill in the art would understand, based on the instant description, that other diseases can also be treated according to the invention.

Description of the Pharmaceutical Compositions and Methods of Administration of the Compounds of the Invention

Pharmaceutically acceptable salts of these compounds as well as commonly used prodrugs of these compounds are also within the scope of the invention.

Salts, especially pharmaceutically acceptable salts, of the compounds of the invention such as, for example, organic or inorganic acid addition salts, are also provided by the invention. Suitable inorganic acids include but are not limited to halogen acids (such as hydrochloric acid), sulfuric acid, or phosphoric acid. Suitable organic acids include but are not limited to carboxylic, phosphonic, sulfonic, or sulfamic acids, with examples including acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, 2- or 3-hydroxybutyric acid, γ-aminobutyric acid (GABA), gluconic acid, glucosemonocarboxylic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azeiaic acid, malic acid, tartaric acid, citric acid, glucaric acid, galactaric acid, amino acids (such as glutamic acid, aspartic acid, N-methylglycine, acetytaminoacetic acid, N-acetylasparagine or N-acetylcysteine), pyruvic acid, acetoacetic acid, phosphoserine, and 2- or 3-glycerophosphoric acid.

Formation of prodrugs is well known in the art in order to enhance the properties of the parent compound; such properties include solubility, absorption, biostability and release

time (see *"Pharmaceutical Dosage Form and Drug Delivery Systems"* (Sixth Edition), edited by Ansel *et al.*, publ. by Williams & Wilkins, pgs. 27-29, (1995)). Commonly used prodrugs of the disclosed 2,4-diamino-pyrimidine compounds can be designed to take advantage of the major drug biotransformation reactions and are also to be considered within the scope of the invention. Major drug biotransformation reactions include N-dealkylation, O-dealkylation, aliphatic hydroxylation, aromatic hydroxylation, N-oxidation, S-oxidation, deamination, hydrolysis reactions, glucuronidation, sulfation and acetylation (see *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff *et al.*, publ. by McGraw-Hill, pages 11-13, (1996)).

The invention also includes pharmaceutical compositions comprising one or more of the compounds of the invention, or their salts or prodrugs forms thereof, with a pharmaceutically acceptable ingredient.

The pharmaceutical compositions can be prepared so that they may be administered orally, dermally, parenterally, nasally, ophthalmically, otically, sublingually, rectally or vaginally. Dermal administration includes topical application or transdermal administration. Parenteral administration includes intravenous, intraarticular, intramuscular, and subcutaneous injections, as well as use of infusion techniques. One or more compounds of the invention may be present in association with one or more non-toxic pharmaceutically acceptable ingredients and optionally, other active anti-proliferative agents, to form the pharmaceutical composition. These compositions can be prepared by applying known techniques in the art such as those taught in *Remington's Pharmaceutical Sciences* (Fourteenth Edition), Managing Editor, John E. Hoover, Mack Publishing Co., (1970) or *Pharmaceutical Dosage Form and Drug Delivery Systems* (Sixth Edition), edited by Ansel *et al.*, publ. by Williams & Wilkins, (1995).

Commonly used pharmaceutical ingredients which can be used as appropriate to formulate the composition for its intended route of administration include:

acidifying agents, examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid;

alkalinizing agents, examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine;

adsorbents, examples include but are not limited to powdered cellulose and activated

charcoal;

aerosol propellants, examples include but are not limited to carbon dioxide, CCl_2F_2, F_2ClC-$CClF_2$ and $CClF_3$;

air displacement agents, examples include but are not limited to nitrogen and argon;

antifungal preservatives, examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate;

antimicrobial preservatives, examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal;

antioxidants, examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite;

binding materials, examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones and styrene-butadiene copolymers;

buffering agents, examples include but are not limited to potassium metaphosphate, potassium phosphate monobasic, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate;

carrying agents, examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection;

chelating agents, examples include but are not limited to edetate disodium and edetic acid;

colorants, examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red;

clarifying agents, examples include but are not limited to bentonite;

emulsifying agents, examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyethylene 50 stearate;

encapsulating agents, examples include but are not limited to gelatin and cellulose acetate phthalate;

flavorants, examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin;

humectants, examples include but are not limited to glycerin, propylene glycol and sorbitol;

levigating agents, examples include but are not limited to mineral oil and glycerin;

oils, examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil;

ointment bases, examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment;

penetration enhancers (transdermal delivery), examples include but are not limited to monohydroxy or polyhydroxy alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas;

plasticizers, examples include but are not limited to diethyl phthalate and glycerin;

solvents, examples include but are not limited to alcohol, corn oil, cottonseed oil, glycerin, isopropyl alcohol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation;

stiffening agents, examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax;

suppository bases, examples include but are not limited to cocoa butter and polyethylene glycols (mixtures);

surfactants, examples include but are not limited to benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan monopalmitate;

suspending agents, examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum;

sweetening agents, examples include but are not limited to aspartame, dextrose, glycerin, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose;

tablet anti-adherents, examples include but are not limited to magnesium stearate and talc;

tablet binders, examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and pregelatinized starch;

tablet and capsule diluents, examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powedered cellulose,

precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch;

tablet coating agents, examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac;

tablet direct compression excipients, examples include but are not limited to dibasic calcium phosphate;

tablet disintegrants, examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, sodium alginate, sodium starch glycollate and starch;

tablet glidants, examples include but are not limited to colloidal silica, corn starch and talc);

tablet lubricants (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate;

tablet/capsule opaquants, examples include but are not limited to titanium dioxide;

tablet polishing agents, examples include but are not limited to carnuba wax and white wax;

thickening agents, examples include but are not limited to beewax, cetyl alcohol and paraffin;

tonicity agents, examples include but are not limited to dextrose and sodium chloride;

viscosity increasing agents, examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, povidone, sodium alginate and tragacanth; and

wetting agents, examples include but are not limited to heptadecaethylene oxycetanol, lecithins, polyethylene sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate.

Depending on the route of administration, the compositions can take the form of aerosols, capsules, creams, elixirs, emulsions, foams, gels, granules, inhalants, lotions, magmas, ointments, peroral solids, powders, sprays, syrups, suppositories, suspensions, tablets and tinctures.

The therapeutic methods of the invention generally comprise administering to a subject in need thereof, a pharmaceutically effective amount of a compound. The compounds of the invention can be administered in a amount effective to inhibit the activity of a kinase, e.g., a tyrosine kinase, such as src kinase. The compounds of the invention can

also be administered in a "growth inhibitory amount," i.e., an amount of the compound which is pharmaceutically effective to inhibit or decrease proliferation of target cells. The compounds can also be administered in a "differentiation modulating amount", e.g., "differentiation-inducing amount" or "differentiation-inhibiting amount," which is an amount of the compound which is pharmaceutically effective to modulate differentiation of target cells. The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

Toxicity and therapeutic efficacy of the compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50}. Compounds which exhibit large therapeutic indices are preferred. While compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such reagents to the site of affected tissue in order to minimize potential damage to normal cells and, thereby, reduce side effects.

Data obtained from cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such reagents lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any reagent used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC_{50} (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Based on these assays, it is possible to derive an appropriate dosage for administration to subjects by combining IC_{50} data with appropriate pharmacokinetic evaluation.

Pharmaceutical compositions containing a compound of the invention may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropylmethyl-cellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate buryrate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with

partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the compound of the invention in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

Pharmaceutical compositions may be in the form of sterile injectable aqueous solutions. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, ethanol, cremophore, and isotonic sodium chloride solution.

Sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the compound of the invention is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulation.

The injectable solutions or microemulsions may be introduced into a patient's blood-stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of the invention may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of the invention can be employed. For purposes of this application, topical application shall include mouth washes and gargles.

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will preferably be continuous rather than intermittent throughout the dosage regimen.

The compounds of the invention may also be co-administered with other well known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. The compounds may be administered simultaneously or sequentially. For example, the instant compounds may be useful in combination with known anti-cancer and cytotoxic agents. Similarly, the instant compounds may be useful in combination with agents that are effective in the treatment and prevention of osteoporosis, inflammation, neurofibromatosis, restinosis, and viral infections. The instant compounds may also be useful in combination with inhibitors of other components of signaling pathways of cell surface growth factor receptors.

Drugs can be co-administered to a subject being treated with a compound of the invention include antineoplastic agents selected from vinca alkaloids, epipodophyllotoxins, anthracycline antibiotics, actinomycin D, plicamycin, puromycin, gramicidin D, taxol, colchicine, cytochalasin B, emetine, maytansine, or amsacrine. Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR), e.g., 1996 edition (Medical Economics Company, Montvale, N.J. 07645-1742, USA).

Optional anti-proliferative agents that can be added to the composition include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11th Edition of the Merck Index, (1996), which is hereby incorporated by reference, such as asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin

(adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other anti-proliferative agents suitable for use with the composition of the invention include but are not limited to those compounds acknowldeged to be used in the treatment of neoplastic diseases in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff *et al.*, publ. by McGraw-Hill, pages 1225-1287, (1996), such as aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2', 2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

Other anti-proliferative agents suitable for use with the composition of the invention include but are not limited to other anti-cancer agents such as epothilone, irinotecan, raloxifen and topotecan.

For all regimens of use disclosed herein for the invention, the daily oral dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

It will be appreciated by those skilled in the art that the particular method of administration will depend on a variety of factors, all of which are considered routinely when

administering therapeutics. It will also be understood, however, that the specific dose level for any given patient will depend upon a variety of factors, including, but not limited to the activity of the specific compound employed, the age of the patient, the body weight of the patient, the general health of the patient, the gender of the patient, the diet of the patient, time of administration, route of administration, rate of excretion, drug combinations, and the severity of the condition undergoing therapy. It will be further appreciated by one skilled in the art that the optimal course of treatment, i.e., the mode of treatment and the daily number of doses of a compound of formulae (I) or (II) or a pharmaceutically acceptable salt thereof given for a defined number of days, can be ascertained by those skilled in the art using conventional treatment tests.

Radiation therapy, including x-rays or gamma rays which are delivered from either an externally applied beam or by implantation of tiny radioactive sources, may also be used in combination with a compound of the invention to treat a disease, e.g., cancer.

When a composition according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

Kits of the invention

In one embodiment, compounds of the invention and/or materials and reagents required for administering the compounds of the invention may be assembled together in a kit. When the components of the kit are provided in one or more liquid solutions, the liquid solution preferably is an aqueous solution, with a sterile aqueous solution being particularly preferred.

The kit may further comprise one or more other drugs, e.g., chemo- or radiotherapeutic agent. These normally will be a separate formulation, but may be formulated into a single pharmaceutically acceptable composition. The container means may itself be geared for administration, such as an inhalant, syringe, pipette, eye dropper, or other such like apparatus, from which the formulation may be applied to an infected area of the body, such as the lungs, or injected into an animal, or even applied to and mixed with the other components of the kit.

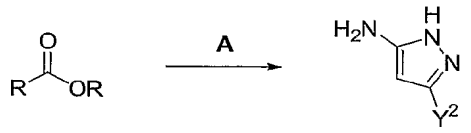
The compositions of these kits also may be provided in dried or lyophilized forms. When reagents or components are provided as a dried form, reconstitution generally is by the addition of a suitable solvent. It is envisioned that the solvent also may be provided in another container means. The kits of the invention may also include an instruction sheet defining administration of the agent and, e.g., explaining how the agent will decrease proliferation of cells.

The kits of the present invention also will typically include a means for containing the vials in close confinement for commercial sale such as, e.g., injection or blow-molded plastic containers into which the desired vials are retained. Irrespective of the number or type of containers, the kits of the invention also may comprise, or be packaged with a separate instrument for assisting with the injection/administration or placement of the ultimate complex composition within the body of an animal. Such an instrument may be an inhalant, syringe, pipette, forceps, measured spoon, eye dropper or any such medically approved delivery vehicle. Other instrumentation includes devices that permit the reading or monitoring of reactions.

The present invention is further illustrated by the following examples which should not be construed as limiting in any way. The contents of all cited references (including literature references, issued patents, published patent applications as cited throughout this application) are hereby expressly incorporated by reference.

Examples 1-101

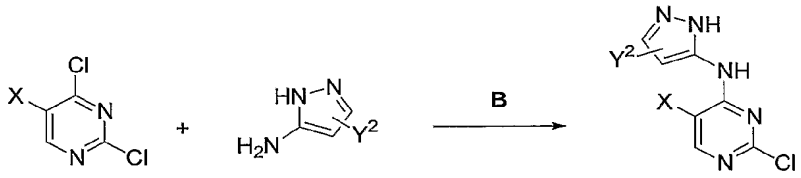
General Method A. Preparation of 5-amino-3-substituted pyrazoles



To a mixture of NaH (2.1 equiv) and THF (0.15 M) is added CH_3CN (2.1 equiv) and the required ester (1 equiv). The suspension is stirred at 65 °C for 16 h. The reaction is then quenched with an alcohol such as EtOH at 0 °C. Volatiles are evaporated and water added to the residue. This solution is cooled to 0 °C and the pH adjusted to ~3 with conc. HCl. The

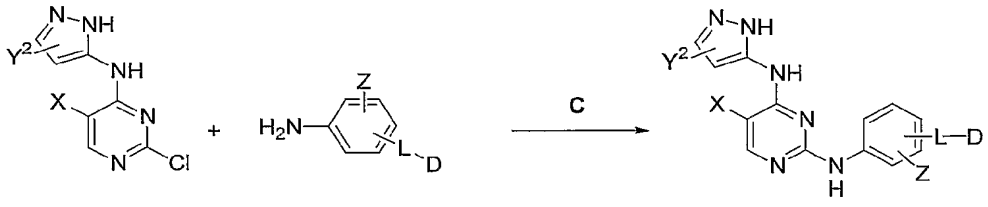
solution is extracted with Et_2O (3x) to give the crude β-ketonitrile intermediate. The crude β-ketonitrile (1 equiv) is treated with EtOH (0.3 M) and hydrazine hydrate (1.3 equiv) and stirred at 70 °C for 15 h. Volatiles are evaporated and the crude residue is purified by flash column chromatography (1/9 $MeOH/CH_2Cl_2$) to give the required pyrazole whose structure is confirmed by LC/MS and ^1H NMR.

General Method B. Coupling of substituted 5-aminopyrazoles with 5-substituted-2,4-dichloropyrimides



A solution of 5-substituted-2,4-dichlorpyrimidine (1 equiv), KOAc (1.3 equiv) and 5-amino-3-substituted pyrazole (1.1 equiv) in THF/H_2O (2/1, 0.15 M) is heated at 40 °C for 24 h. The reaction mixture is allowed to cool to rt, dissolved in EtOAc and washed with aqueous $NaHCO_3$. The combined organic layers are dried ($MgSO_4$) and concentrated under reduced pressure. The resulting crude solid is purified either by silica gel column chromatography or washing with other solvents to afford the *N*-(3-substituted-1*H*-pyrazol-5-yl)-2-chloro-5-substituted-4-pyrimidinamine intermediate whose structure is confirmed by LC/MS and ^1H NMR.

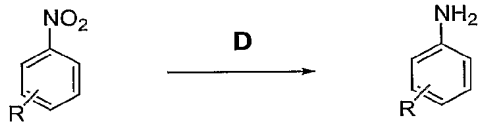
General Method C. Coupling of substituted anilines with *N*-(3-substituted-1*H*-pyrazol-5-yl)-2-chloro-5-substituted-4-pyrimidinamines



A solution of *N*-(3-substituted-1*H*-pyrazol-5-yl)-2-chloro-5-substituted-4-pyrimidinamine (1 equiv) and a substituted aniline (1 equiv) in an alcohol such as *n*-BuOH (0.08 M) with a

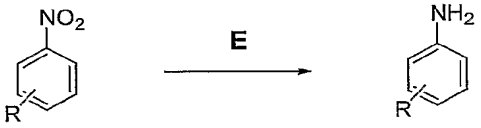
catalytic amount of conc. HCl is heated at 100 °C for 24 h. The reaction is cooled to rt then concentrated under reduced pressure. The crude residue is dissolved in CH_2Cl_2 and washed with aqueous $NaHCO_3$. The combined organic layers are dried ($MgSO_4$) and concentrated under reduced pressure. Preparative thin-layer silica gel chromatography, silica gel column chromatography, and/or preparative HPLC are used to purify final products. LC/MS and ^1H NMR spectroscopy are used to confirm the structures of the final 2,4-substituted pyrimidinediamines.

General Method D. Hydrogenation of substituted nitrobenzenes with palladium to substituted anilines



A solution of the substituted nitrobenzene (1 equiv) in ethanol (0.2 M) is added via syringe to a flask containing palladium on carbon (10 mol%). The reaction vessel is fitted with a balloon adapter and charged with hydrogen and evacuated three times until the reaction is under a H_2 atmosphere. The reaction is allowed to stir overnight and then purged with Ar and evacuated three times until an Ar atmosphere had been achieved. The reaction solution is filtered through a pad of Celite and washed with copious amounts of ethanol. The filtrate is concentrated in vacuo to afford the desired aniline whose structure is confirmed by LC/MS and ^1H NMR.

General Method E. Reduction of substituted nitrobenzenes with tin chloride to substituted anilines



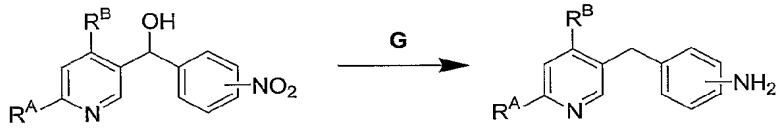
A solution of intermediate nitro derivative (1 equiv) and $SnCl_2$ (6 equiv) in ethanol (0.18 M) is heated to reflux over 4h. The reaction mixture is allowed to cool to rt, concentrated and

dissolved in EtOAc. Satd $NaHCO_3$ is then added to precipitate the tin salts. The liquid is decanted and poured into a separatory funnel and diluted with EtOAc and washed with H_2O. The combined organic layers are dried ($MgSO_4$) and filtered. The filtrate is concentrated in vacuo to afford the intermediate aniline whose structure is confirmed by LC/MS and ^1H NMR.

General Method F. Preparation of substituted (nitrophenyl)(3-pyridinyl)methanols

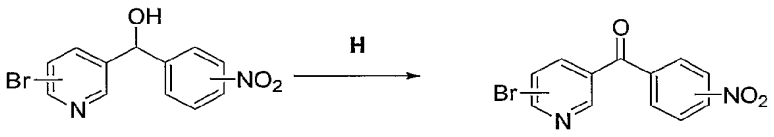
To a 0 °C solution of the 3-bromopyridine derivative (1 equiv) in THF (1 M) is added isopropyl magnesium chloride (1 equiv, 2.0 M solution in THF). The mixture is allowed to warm up to ambient temperature and stir for 2 h. A solution of 3- or 4-nitrobenzaldehyde (1 equiv) in THF (1 M) is then added and the reaction mixture is left to stir at rt for 15 h. The reaction is quenched with H_2O and extracted with CH_2Cl_2 (3x). The organic layer is dried (Na_2SO_4) and purified using column chromatography (MeOH/ CH_2Cl_2 1:20) to give a yellow solid whose structure is confirmed by LC/MS and ^1H NMR.

General Method G. Preparation of (3-pyridinylmethyl)anilines



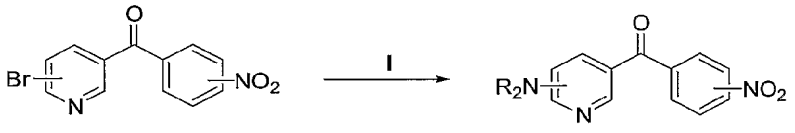
The pyridylcarbinol is dissolved in MeOH/AcOH (3:1) and is added via syringe to a flask containing 10% Pd/C (20% w/w). The reaction vessel is fitted with a balloon adapter and charged with hydrogen and evacuated three times until the reaction is under a H_2 atmosphere. The reaction is allowed to stir overnight and then purged with Ar and evacuated three times until an Ar atmosphere has been achieved. The reaction solution is filtered through a pad of Celite and washed with copious amounts of ethanol. The filtrate is concentrated in vacuo to afford the desired aniline which is confirmed by LC/MS and ^1H NMR.

General method H. Preparation of substituted (bromo-3-pyridinyl)(nitrophenyl)-methanones



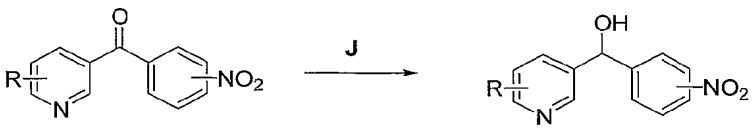
To a solution of a 2-bromopyridylcarbinol (1 equiv) in THF (0.03 M) is added MnO_2 (4x w/w) and the suspension is stirred at 60 °C for 2 h. The reaction mixture is cooled to rt then filtered through a pad of Celite and washed with CH_2Cl_2 to afford a yellow solid whose structure is confirmed by LC/MS and ^1H NMR.

General Method I. Preparation of substituted (amino-3-pyridinyl)(nitrophenyl)-methanones



The ketone (1 equiv) is treated with the required primary or secondary amine (3 equiv) in pyridine (0.04 M) and heated to 100 °C until TLC indicates completion of the reaction. Evaporation of volatiles followed by column chromatography (EtOAc/hexanes) yields the product whose strucuture is confirmed by LC/MS and ^1H NMR.

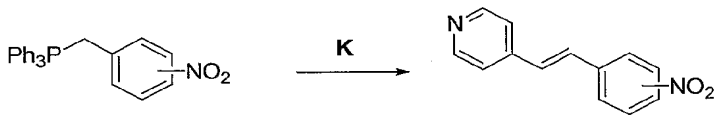
General procedure J. Preparation of substituted (4-nitrophenyl)(3-pyridinyl)-methanols



The 2-substituted pyridyl ketone (1 equiv) is dissolved in MeOH/THF (3:1) and cooled to 0

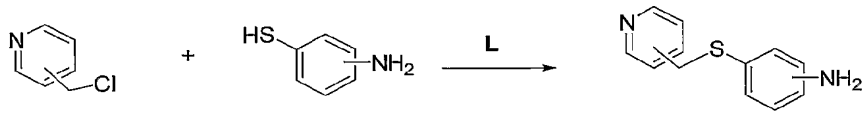
°C before addition of $NaBH_4$ (10 equiv) is carried out. The reaction is then warmed to ambient temperature and allowed to stir for 15 h. The reaction mixture is halved by evaporation of volatiles and quenched with silica gel. The mixture is purified by column chromatography (EtOAc/hexanes 8:2) to give the 2-substitutedpyridyl carbinol derivatives whose structures are confirmed by LC/MS and ^1H NMR.

General procedure K. Preparation of substituted [(Œ)-(nitrophenyl)ethenyl]pyridines



To an oven dried 3-neck flask is added (nitrobenzyl)triphenylphosphonium bromide (1.2 equiv) followed by the addition of THF (0.3 M). The solution is cooled to 0 °C in an ice bath. Potassium *t*-butoxide (1.3 equiv) is then added in one portion resulting in an orange suspension. The suspension is maintained at 0 °C while a solution of 4-pyridine carboxyaldehyde (1 equiv) in THF (1.2 M) is added over 10 minutes. The ice bath is removed and the reaction is stirred at room temperature for 2 h. At this time, the reaction is quenched with saturated NH_4Cl solution and stirred for 15 min. The mixture is then extracted with EtOAc (2x) and the combined extracts are washed with brine and dried ($MgSO_4$). The solvent is removed at reduced pressure and the residue is purified by column chromatography using 0-50% EtOAc in hexanes as eluent to afford the desired alkene intermediate whose structure is confirmed by ^1H NMR.

General procedure L. Preparation of sustituted [(pyridinylmethyl)sulfanyl]anilines



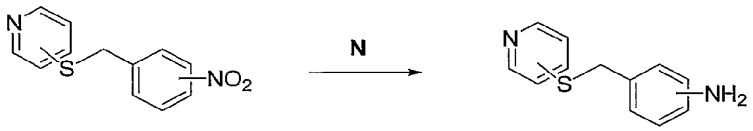
To a solution of aminothiophenol (1 equiv) in anhydrous DMF (0.8 M) is added (chloromethyl)pyridine (1 equiv) followed by K_2CO_3 (2 equiv). The reaction mixture is heated at 80 °C overnight, then diluted with ethyl acetate and water. The aqueous layer is

back-extracted with ethyl acetate (2 x). The combined organic layers are washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue is filtered through a pad of silica eluting with EtOAc. The resulting material is triturated with a Et_2O/hexane solution to afford the desired aniline whose structure is confirmed by ^1H NMR.

General procedure M. Preparation of substituted [(nitrophenyl)sulfanyl]methylpyridines

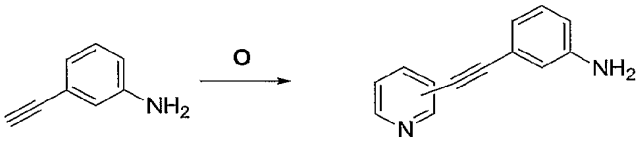
To a solution of pyridinethiol (1 equiv) in anhydrous DMF (0.8 M) is added nitrobenzyl chloride (1 equiv) followed by K_2CO_3 (2 equiv). The reaction mixture is heated at 80 °C overnight, then diluted with ethyl acetate and water. The aqueous layer is back-extracted with ethyl acetate (2 x). The combined organic layers are washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue is filtered through a pad of silica eluting with EtOAc. The resulting material is triturated with a Et_2O/hexane solution to afford the desired aniline whose structure is confirmed by ^1H NMR.

General procedure N. Preparation of substituted [(pyridinylsulfanyl)methyl]anilines



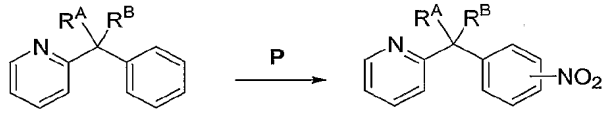
A slurry of the nitro compound (1 equiv), iron powder (4 equiv), acetic acid (0.25 M), and water (1% of the volume) are stirred at ambient temperature overnight. The mixture is diluted with Et_2O and water. The aqueous phase is adjusted to pH 5 with a 4 N NaOH solution. The combined organic layers are washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue is purified by column chromatography using 50% EtOAc/hexanes as eluent to afford the desired aniline whose structure is confirmed by ^1H NMR.

General procedure O. Preparation of substituted 3-(pyridinylethynyl)anilines



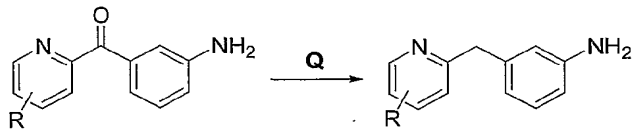
A mixture of aminiophenyl propyne (1 equiv), bromopyridine (1.1 equiv), copper(I) iodide (0.25 equiv), triphenylphosphine (0.25 equiv), and *trans*-dichlorobis(triphenylphosphine)palladium(II) (0.25 equiv) in DMF (0.5 M) and Et_3N (0.8 M) is stirred at 80 °C under argon overnight. The mixture is cooled to ambient temperature and diluted with EtOAc and water. The layers are separated and the organic phase is washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by column chromatography using 30-70% EtOAc in hexanes as eluent affords the alkyne intermediate whose structure is confirmed by LC/MS and ^1H NMR.

General procedure P. Preparation of (nitrophenyl)(2-pyridinyl)methanones and 2-nitrophenylmethylpyridines



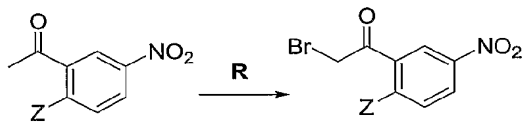
A solution of benzoylpyridine (1 equiv) in concentrated H_2SO_4 (0.78 M) is cooled to 0 °C and treated with potassium nitrate (1 equiv) in portions. The reaction mixture is warmed slowly to room temperature over 2 h and poured over ice. The solution is then basified with NH_4OH and extracted with EtOAc. The extract is washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue is treated with Et_2O and the precipitated solid is filtered to afford the desired nitro intermediate whose structure is confirmed by ^1H NMR.

General procedure Q. Preparation of substituted (pyridinylmethyl)anilines



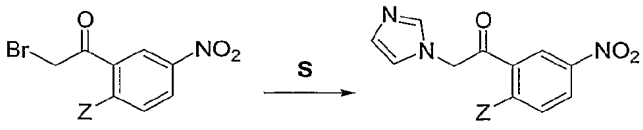
A mixture of the starting ketone (1 equiv), hydrazine hydrate (30 equiv), and KOH (8 equiv) in ethylene glycol (0.3 M) is heated to 180 °C in a sealed tube overnight. The reaction is cooled to room temperature, diluted with CH_2Cl_2, washed with H_2O, brine, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by column chromatography using 60-80% EtOAc in hexanes as eluent affords the desired aniline whose structure is confirmed by ^1H NMR.

General procedure R. Preparation of substituted 2-bromo-1-(3-nitrophenyl)ethanones



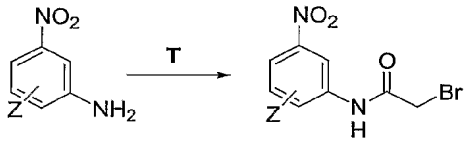
A solution of substituted acetophenone (1 equiv) in THF (0.47 M) is cooled to 0 °C under argon and treated with phenyltrimethylammonium tribromide (1 equiv). The reaction is stirred and allowed to warm up slowly to room temperature over 2 h. The reaction is quenched with H_2O and diluted with Et_2O. The layers are separated and the organic phase is washed with brine, dried ($MgSO_4$), and concentrated at reduced pressure. The solid obtained is washed with a solution of Et_2O/hexanes to afford the desired α-bromoketone whose structure is confirmed by ^1H NMR.

General procedure S. Preparation of substituted 2-(1H-imidazol-1-yl)-1-(3-nitrophenyl)ethanones



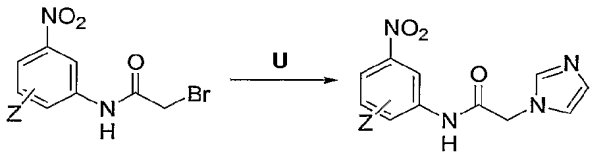
A solution of the α-bromoketone (1 equiv) in THF (0.3 M) is cooled to 0 °C under argon. Imidazole (1 equiv) is added to the reaction, followed by the addition of Et_3N (3 equiv). The reaction is warmed to room temperature and stirred overnight. The reaction is then diluted with EtOAc, washed with H_2O, brine, dried ($MgSO_4$), and concentrated at reduced pressure. Purification by column chromatography using 2% MeOH in CH_2Cl_2 as eluent affords the desired nitro intermediate whose structure is confirmed by 1H NMR.

General procedure T. Preparation of substituted 2-bromo-N-(3-nitrophenyl)-acetamides



A suspension of the nitroaniline (1 equiv) and $NaHCO_3$ (4 equiv) in $CHCl_3$ (1 M) is cooled to 0 °C. Bromoacetyl bromide (1.1 equiv) is added dropwise and the resulting thick suspension is stirred at 0 °C for 30 min. The reaction is then diluted with CH_2Cl_2 and water. The layers are separated and the organic phase is washed with brine, dried ($MgSO_4$), and concentrated at reduced pressure to furnish the intermediate nitro-α-bromoamide derivative whose structure is confirmed by ^1H NMR.

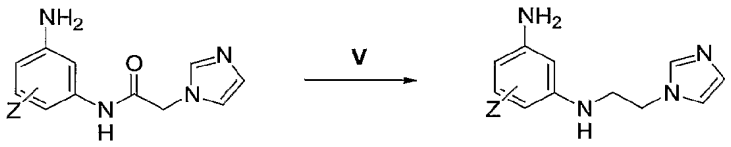
General Procedure U. Preparation of substituted 2-(1H-imidazol-1-yl)-N-(3-nitrophenyl)acetamides



A solution of the α-bromo acetamide (1 equiv), imidazole (2 equiv) and K_2CO_3 (8 equiv) in acetone (0.10 M) is heated to 65 °C for 24 h. The reaction mixture is allowed to cool to room temperature, diluted with EtOAc and washed with H_2O. The organic layer is concentrated in vacuo and the resulting crude solid or oil is purified by silica gel column

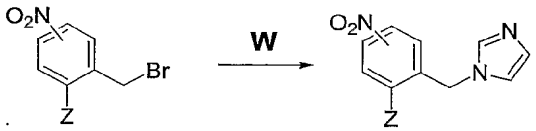
chromatography to furnish the intermediate nitro derivative whose structure is confirmed by LC/MS and ^{1}H NMR.

General procedure V. Preparation of substituted [2-(1H-imidazol-1-yl)ethyl]-1,3-benzenediamines



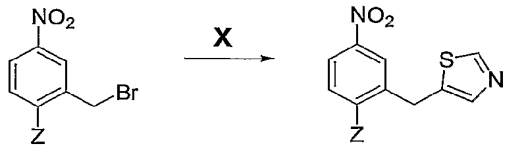
A solution of the amide (1 equiv) in THF (0.1 M) is treated with borane dimethylsulfide (5 equiv). The reaction mixture is refluxed under argon overnight at which time it becomes a suspension. The reaction mixture is cooled to room temperature and quenched with EtOH (15 equiv) and 2 M HCl (6 equiv). The resulting solution is refluxed for 1 h, cooled to room temperature, and basified with 1 N KOH solution. The product is then extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated at reduced pressure to give crude product. Purification by column chromatography using 2-8% MeOH in CH_2Cl_2 as eluent affords the aniline intermediate whose structure is confirmed by ^{1}H NMR.

General Method W. Preparation of substituted 1-(3-nitrobenzyl)-1H-imidazoles



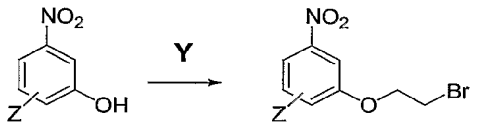
A solution of imidazole (2 equiv) and nitrobenzyl bromide (1 equiv) in anhydrous THF (0.20 M) is stirred under argon for 15 h. The resulting white precipitate is filtered off and the filtrate is concentrated *in vacuo*. The reaction is partitioned between H_2O and CH_2Cl_2. The organic layer is washed with brine and concentrated under reduced pressure to afford an oil. The crude residue is purified by silica gel chromatography to afford the aminobenzene derivative whose structure is confirmed by LC/MS and ^{1}H NMR.

General Method X. Preparation of substituted 5-(3-nitrobenzyl)-1,3-thiazoles



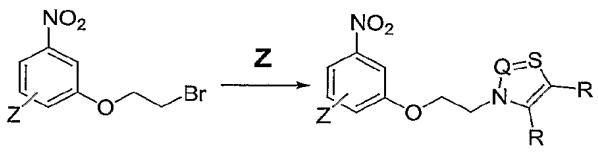
A solution of 3-nitrobenzylbromide (1 equiv) and thiazole (3 equiv) in DCE (0.46 M) is added dropwise to a suspension of AgOTf (1.2 equiv) in DCE (0.11 M) at ambient temperature. The flask is covered to protect it from light and allowed to stir overnight under Ar. The mixture is filtered to remove Ag salts and the filtrate is diluted with CH_2CH_2. The combined organics are washed with H_2O and dried (Na_2SO_4) before being concentrated *in vacuo*. The residue is triturated with hexanes and the pink-red solid is dried under high vacuum. No further purification is performed and LC/MS and ^1H NMR confirms the structure of the nitro intermediate.

General Method Y. Preparation of substituted 1-(2-bromoethoxy)-3-nitrobenzenes



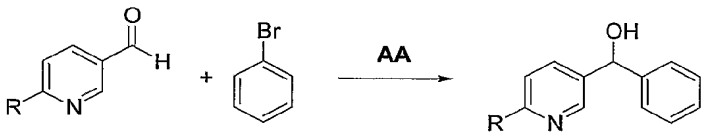
A solution of substituted nitrophenol (1 equiv) in CH_3CN (0.72 M) is added 1,2-dibromoethane (1 equiv) and Cs_2CO_3 (3 equiv). The mixture is refluxed overnight. After cooling to ambient temperature, the reaction mixture is diluted by EtOAc and washed with 1N NaOH (3x), water (1x) and brine (2x). The organic layer is dried ($MgSO_4$) and concentrated in vacuo to afford the crude product whose structure is confirmed by ^1H NMR and used without further purification.

General Method Z. Preparation of substituted aromatic heterocyclic 3-nitrobenzenes



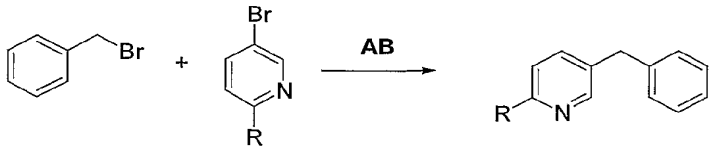
A solution of bromoether intermediate (1 equiv), heterocycle (2 equiv) and K_2CO_3 (8 equiv) in acetone (0.10 M) is heated to 65 °C for 24 h. The reaction mixture is allowed to cool to ambient temperature, diluted with EtOAc and washed with H_2O. The organic layer is concentrated in vacuo and the resulting crude solid or oil is purified by silica gel column chromatography to furnish the intermediate heterocyclic-substituted nitro derivatives whose structure is confirmed by LC/MS and ^{1}H NMR.

General procedure AA. Preparation of substituted phenyl(3-pyridinyl)methanols



Bromobenzene (1 equiv) is dissolved in THF (0.15 M) and cooled to –78 °C. A 1.6 M solution of *n*-BuLi in THF (1.2 equiv) is added via syringe and the mixture is allowed to stir for 45 min. A solution of the pyridinecarboxaldehyde (1.2 equiv) in THF (0.7 M) is added and the reaction is stirred at –78 °C for 75 min. The cold bath is removed and the reaction is stirred for an additional 15 min followed by quenching with aq NH_4Cl at 0 °C. The quenched reaction mixture is dissolved in CH_2Cl_2, transferred to a separatory funnel and washed with brine (2x). The aqueous portion is back extracted with CH_2Cl_2 (2x) and the combined organics are dried ($MgSO_4$), filtered and concentrated. The crude residue is purified by flash silica gel chromatography to afford the desired alcohol, which is confirmed by LC/MS and ^{1}H NMR.

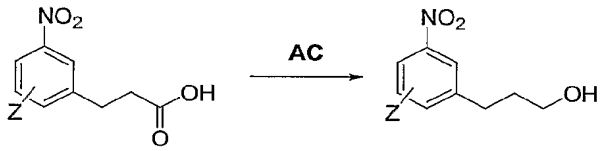
General procedure AB. Preparation of substituted 3-benzylpyridines



Dibromoethane (0.02 equiv) is added to a suspension of Zn dust (4 equiv) in THF (0.1 M)

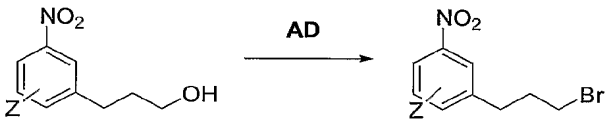
and heated to 60 °C for 3 min then immediately cooled to 35 °C. TMSCl (0.57 equiv) is added via syringe and the reaction is maintained at 35 °C for 30 min. Benzyl bromide (1.03 equiv) is added via syringe and the solution is stirred an additional 30 min at 35 °C. The bromopyridine (1 equiv) and $Pd(PPh_3)_4$ (0.003 equiv) are added and the reaction is heated to 50 °C overnight. The reaction mixture is cooled, filtered through a pad of Celite, transferred to a separatory funnel and washed with 1N HCl (1x) then extracted with CH_2Cl_2 (3x). The combined organics are dried ($MgSO_4$), filtered and concentrated. The crude residue is purified by flash silica chromatography to afford the desired pyridine intermediate whose structure is confirmed by LC/MS and ^1H NMR.

General Method AC. Preparation of substituted 3-(nitrophenyl)-1-propanols



A solution of the nitrophenyl propionic acid (1 equiv) in THF (2.0 M) is cooled to 0 °C and 1.0 M BH_3·THF (1.3 equiv) is added slowly via syringe. The cold bath is removed and the reaction is allowed to reach room temperature and stir an additional 2 h. The reaction is quenched slowly with cold water, dissolved in Et_2O, transferred to a separatory funnel and washed with aqueous $NaHCO_3$ (1x) then brine (1x). The combined organics are dried ($MgSO_4$), filtered and concentrated in vacuo and the resulting crude solid or oil is purified by silica gel column chromatography to furnish the intermediate alcohol derivative whose structure is confirmed by LC/MS and ^1H NMR.

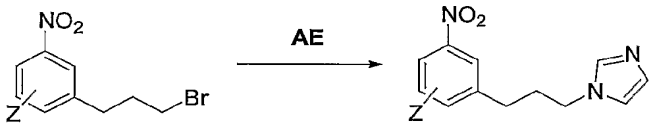
General Method AD. Preparation of substituted (3-bromopropyl)nitrobenzenes



A solution of the nitrophenyl alcohol intermediate (1 equiv), CBr_4 (1.3 equiv), PPh_3 (1.3 equiv) in THF (0.30 M) is stirred at room temperature overnight. The reaction mixture is evaporated to dryness and the resulting crude solid or oil is purified by silica gel column

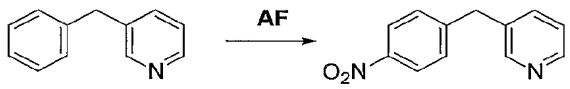
chromatography to furnish the intermediate bromide derivative whose strucute is confirmed by LC/MS and ^{1}H NMR.

General Method AE. Preparation of substituted [3-(nitrophenyl)propyl]-1H-imidazoles



A solution of the nitrophenyl bromide intermediate (1 equiv), imidazole (5 equiv), NaI (1 equiv), and K_2CO_3 (5 equiv) in acetone (0.10 M) is heated to 65 °C for 24 h. The reaction mixture is allowed to cool to ambient temperature, evaporated to dryness, diluted with EtOAc, and washed with H_2O. The organic layer is concentrated in vacuo and the resulting crude solid or oil is purified by silica gel column chromatography to furnish the intermediate nitrophenyl imidazole derivative whose structure is confirmed by LC/MS and ^{1}H NMR.

General procedure AF. Preparation of 3-(4-nitrobenzyl)pyridine



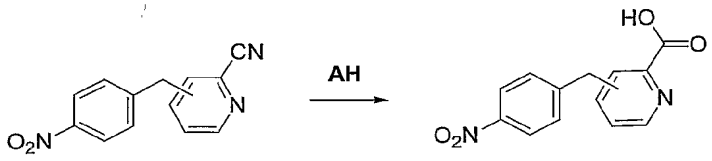
A solution of 3-benzylpyridine (1 equiv) and 70% nitric acid (0.79 M) is heated at 50 °C overnight. The resulting mixture is allowed to cool to ambient temperature before being poured into ice water. The aqueous mixture is then made basic with 1N NaOH and extracted with Et_2O (4x). The combined extracts are sequentially washed with H_2O (3x) and brine before being dried (Na_2SO_4) and concentrated *in vacuo*. The residue is purified by silica gel chromatography (EtOAc/hex, 1:1) then recrystallization affording the nitroaromatic product whose structure is confirmed by LC-MS and ^{1}H NMR.

General Method AG. Preparation of substituted (4-nitrobenzyl)-2-pyridinecarbonitriles

To a solution of nitrobenzyl pyridine (1 equiv) in CH_2Cl_2 (0.2 M) is added MCPBA (1.6 equiv). The solution is stirred at ambient temperature for 2 h. The reaction mixture is then diluted with CH_2Cl_2 and washed with 1N NaOH (2x) and water (1x). The organic layer is dried over Na_2SO_4, filtered, and concentrated in vacuo. The *N*-oxide nitrobenzyl pyridine is a pale yellow solid confirmed by LC/MS and ^1H NMR.

The *N*-oxide nitrobenzyl pyridine intermediate (1 equiv) is dissolved in Et_3N (0.2 M). The solution is stirred under Ar for 5 min and then TMSCN (3 equiv) is carefully added. The solution is heated to 90 °C for 3 h. After cooling to ambient temperature, the solvent is concentrated in vacuo. The crude material is diluted with EtOAc and then washed with brine (1x) followed by H_2O (1x). The organic layer is collected and dried over Na_2SO_4. The material is then purified by column chromatography (1/1 hexane/EtOAc). The nitrobenzyl pyridinecarbonitrile product is confirmed by LC/MS and ^1H NMR.

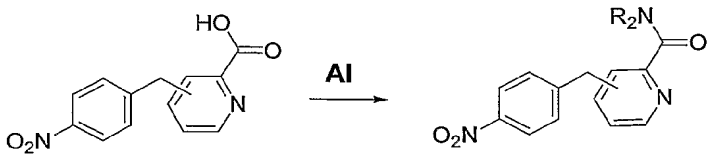
General Method AH. Preparation of substituted (4-nitrobenzyl)-2-pyridinecarboxylic acids



To a solution of nitrobenzyl pyridinecarbonitrile in water (0.05 M) is added a solution of concentrated H_2SO_4/H_2O (6/5) dropwise. The solution is heated to reflux while stirring under Ar for 4 h. Upon cooling to ambient temperature, the solution is washed with CH_2Cl_2 (3x), basified with NaOH to pH~2, and then extracted with EtOAc (3x). The organic layers are combined and dried over Na_2SO_4. The structure of the crude nitrobenzyl pyridinecarboxylic acid is confirmed by LC/MS and ^1H NMR.

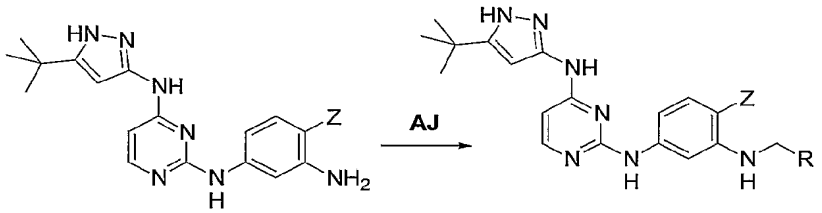
General Method AI. Preparation of substituted (4-nitrobenzyl)-2-

pyridinecarboxamides



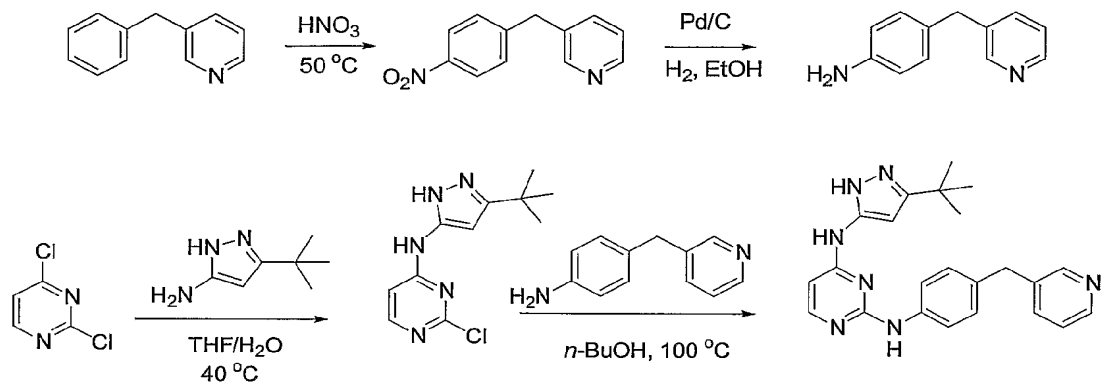
To a solution of nitrobenzyl pyridinecarboxylic acid (1 equiv) in DMF (0.1 M) is added the appropriate amine (1.05 equiv) followed by DMAP (1.2 equiv), NMM (1.05 equiv), and EDCI (1.05 equiv). The solution is stirred at ambient temperature for 24 h. The reaction mixture is then diluted with CH_2Cl_2 and washed with H_2O (1x), 1N HCl (1x), and 1N NaOH (1x). The crude material is then purified by silica gel chromatography using 95/5 CH_2Cl_2/MeOH as the eluent. LC/MS and 1H NMR confirms the structure of the nitrobenzyl pyridine carboxamide derivatives.

General procedure AJ. Preparation of substituted *N*4-(5-tert-butyl-1*H*-pyrazol-3-yl)-*N*2-[substituted phenyl]-2,4-pyrimidinediamines



A solution of the aniline (1 equiv) in EtOH (0.15 M) is treated with the appropriate aldehyde (1 equiv, RCHO) and catalytic amount of *p*-toluenesulfonic acid. The reaction is stirred at ambient temperature overnight. At this time, the reaction is treated with a 1 M solution of $NaCNBH_3$ in THF (2 equiv) and stirring is continued for another 16 h. The reaction is diluted with EtOAc, washed with water, brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product is purified by column chromatography using 70-100% EtOAc in hexanes as eluent to afford the desired product whose structure is confirmed by LC/MS and ^1H NMR.

Example 1: Preparation of N^4-(3-tert-butyl-1H-pyrazol-5-yl)-N^2-[4-(3-pyridinylmethyl)-phenyl]-2,4-pyrimidinediamine.



A solution of 3-benzylpyridine (1 equiv) and 70% nitric acid (0.79 M) was heated at 50 °C overnight. The resulting mixture was allowed to cool to ambient temperature before being poured into ice water. The aqueous mixture was then made basic with 1N NaOH and extracted with Et_2O (4x). The combined extracts were sequentially washed with H_2O (3x) and brine before being dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc/hex, 1:1) then recrystallization affording nitroaromatic product whose structure was confirmed by LC-MS and ^1H NMR.

A solution of the substituted nitrobenzene (1 equiv) in ethanol (0.2 M) is added via syringe to a flask containing palladium on carbon (10 mol%). The reaction vessel is fitted with a balloon adapter and charged with hydrogen and evacuated three times until the reaction is under a H_2 atmosphere. The reaction is allowed to stir overnight and then purged with Ar and evacuated three times until an Ar atmosphere had been achieved. The reaction solution is filtered through a pad of Celite and washed with copious amounts of ethanol. The filtrate is concentrated in vacuo to afford the desired aniline whose structure is confirmed by LC/MS and ^1H NMR.

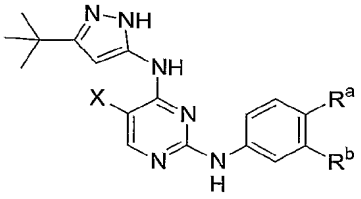
A solution of 2,4-dichloropyrimidine (11.92 g, 80.0 mmol), KOAc (9.42 g, 96.0 mmol, 1.2 equiv) and 5-amino-3-*tert*-butylpyrazole (11.14 g, 80.0 mmol) in THF/H_2O (225 mL, 2/1) was heated at 45 °C for 24 h. The reaction mixture was allowed to cool to ambient temperature, dissolved in EtOAc (200 mL) and washed with aqueous $NaHCO_3$ (2 x 200 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure.

The resulting crude solid was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$, 1/19) to give 8.62 g (43%) of *N*-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-2-chloro-4-pyrimidinamine. ^1H NMR (300 MHz, DMSO) δ 12.2 (s, 1H), 10.3 (s, 1H), 8.16 (s, 1 H), 1.26 (s, 9H); mp>250 °C; MS (ESI-MS) 252 $[M+H]^+$; t_R 2.20 min (10-90% CH_3CN/H_2O).

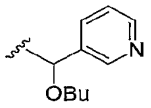
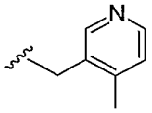
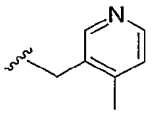
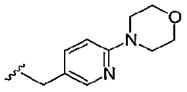
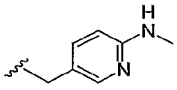
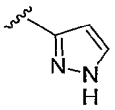
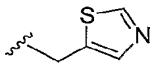
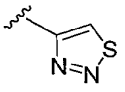
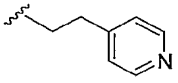
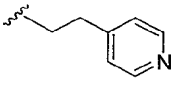
A solution of *N*-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-2-chloro -4-pyrimidinamine (1.5 g, 5.96 mmol), 4-(3-pyridinylmethyl)aniline (1.15 g, 6.24 mmol), and conc. HCl (0.5 mL, 6 mmol) in *n*-BuOH (25 mL) was heated at 70 °C under argon overnight. TLC showed complete conversion of stating material to product. The reaction mixture was cooled to room temperature, diluted with EtOAc, and basified with saturated $NaHCO_3$. The layers were separated and the organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by column chromatography using 1-6% MeOH in CH_2Cl_2 as eluent. It afforded 1.2 g (50%) of N^4-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-N^2-[4-(3-pyridinylmethyl)phenyl]-2,4-pyrimidine-diamine as a white solid. ^1H NMR (300 MHz, CD_3OD) δ 8.43 (d, J = 1.4 Hz, 1H), 8.37 (dd, J = 1.6 and 5.0 Hz, 1H), 7.91-7.89 (m, 1H), 7.70-7.67 (m, 1H), 7.56 (d, J = 8.5 Hz, 2H), 7.38-7.33 (m, 1H), 7.16-7.13 (m, 2H), 6.33-6.25 (m, 2H), 3.99 (s, 2H), 1.27 (s, 9H); MS (EI-LRMS) 400 $[M+H]^+$; t_R 1.84 min; Elemental Analysis for $C_{23}H_{25}N_7 \cdot 0.1H_2O$ calculated: %C 68.84, %H 6.28, %N 24.43; Found: %C 68.75, %H 6.27, %N 24.43.

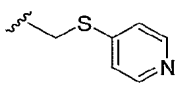
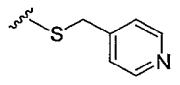
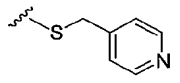
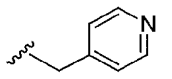
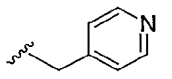
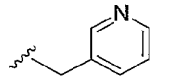
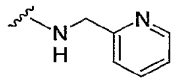
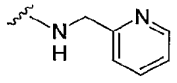
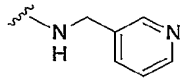
The compounds of examples 2-90 were prepared by general method C where a heterocyclic substituted pyrimidine (prepared by general methods A and B) is reacted with an aniline sidechain (prepared by general methods D-AJ):

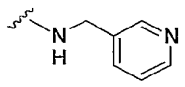
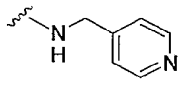
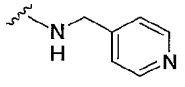
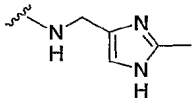
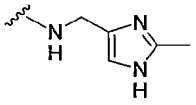
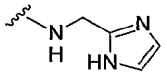
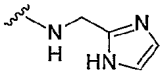
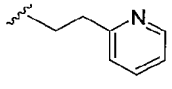
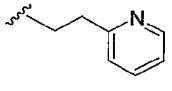
Table 1. Compounds Prepared by general method C.

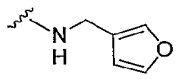
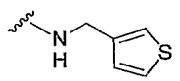
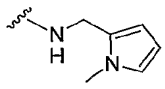
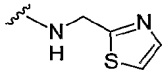
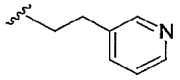
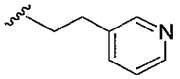
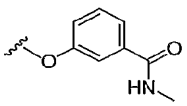
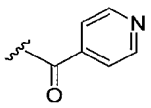
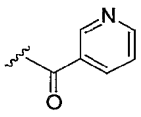


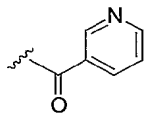
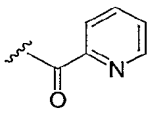
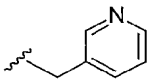
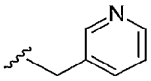
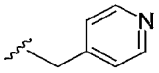
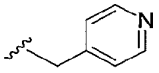
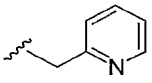
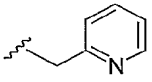
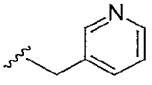
Example #	X	R^a	R^b	Preparation of Aniline Sidechain	Characterization[a]

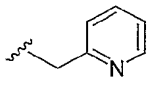
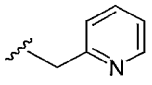
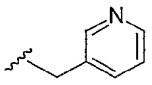
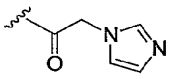
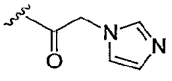
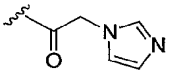
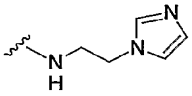
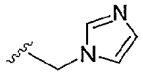
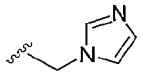
2	H		H	F, D[d]	$(M+H)^+$ 472 R_f = 0.32 (9/1 CH_2Cl_2/MeOH)
3	H	H		F, G	$(M+H)^+$ 414 R_f = 0.4 (9/1 CH_2Cl_2/MeOH)
4	F	H		F, G	$(M+H)^+$ 432 R_f = 0.20 (20/1 CH_2Cl_2/MeOH)
5	H		H	F, H, I, J, G	$(M+H)^+$ 485 R_f = 0.20 (20/1 CH_2Cl_2/MeOH)
6	H		H	F, H, I, J, G	$(M+H)^+$ 429 R_f = 0.37 (9/1 CH_2Cl_2/MeOH)
7	H	H		Commercial (Apollo-Chem	$(M+H)^+$ 375 R_f = 0.15 (9/1 CH_2Cl_2/MeOH)
8	H	H		X, D	$(M+H)^+$ 406 R_f = 0.03 (1/1 CH_2Cl_2/MeOH)
9	H		H	Commercial (Maybridge)	$(M+H)^+$ 393 R_f = 0.50 (19/1 EtOAc/MeOH)
10	H		H	K, D	$(M+H)^+$ 414 R_f = 0.18 (95/5 CH_2Cl_2/MeOH)
11	F		H	K, D	$(M+H)^+$ 432 R_f = 0.16 (95/5 CH_2Cl_2/MeOH)

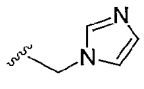
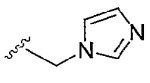
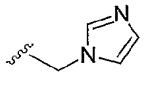
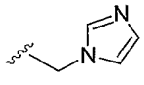
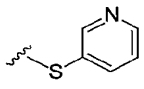
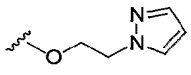
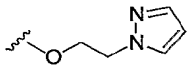
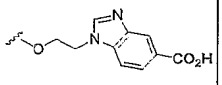
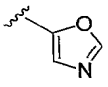
12	H		H	M, N	$(M+H)^+$ 432 R_f = 0.19 (94/6 CH_2Cl_2/MeOH)
13	H		H	L	$(M+H)^+$ 432 R_f = 0.17 (94/6 CH_2Cl_2/MeOH)
14	F		H	L	$(M+H)^+$ 450 R_f = 0.15 (94/6 CH_2Cl_2/MeOH)
15	H		H	Commercial (Maybridge)	$(M+H)^+$ 400 R_f = 0.14 (94/6 CH_2Cl_2/MeOH)
16	F		H	Commercial (Maybridge)	$(M+H)^+$ 418 R_f = 0.10 (96/4 CH_2Cl_2/MeOH)
17	F		H	AF	$(M+H)^+$ 418 R_f = 0.14 (94/6 CH_2Cl_2/MeOH)
18	H	H		D, AJ	$(M+H)^+$ 415 R_f = 0.45 (94/6 EtOAc/MeOH)
19	F	H		D, AJ	$(M+H)^+$ 433 R_f = 0.23 (1/4 Hex/EtOAc)
20	H	H		D, AJ	$(M+H)^+$ 415 R_f = 0.14 (98/2 EtOAc/MeOH)

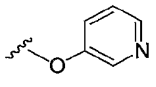
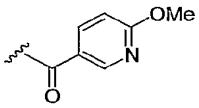
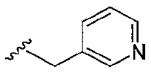
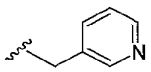
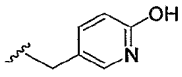
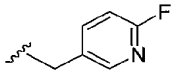
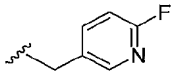
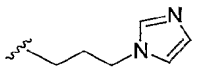
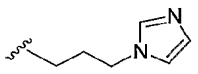
21	F	H		D, AJ	$(M+H)^+$ 433 R_f = 0.10 (1/4 CH_2Cl_2/EtOAc
22	H	H		D, AJ	$(M+H)^+$ 415 R_f = 0.11 (EtOAc)
23	F	H		D, AJ	$(M+H)^+$ 433 R_f = 0.09 (1/4 CH_2Cl_2/EtOAc
24	F	H		D, AJ	$(M+H)^+$ 436 R_f = 0.21 (9/1 CH_2Cl_2/MeOH)
25	H	H		D, AJ	$(M+H)^+$ 418 R_f = 0.23 (85/15 CH_2Cl_2/MeOH)
26	H	H		D, AJ	$(M+H)^+$ 404 R_f = 0.19 (9/1 CH_2Cl_2/MeOH)
27	F	H		D, AJ	$(M+H)^+$ 422 R_f = 0.55 (9/1 EtOAc/MeOH)
28	H	H		O, D	$(M+H)^+$ 414 R_f = 0.28 (92/8 CH_2Cl_2/MeOH)
29	F	H		O, D	$(M+H)^+$ 432 R_f = 0.25 (92/8 CH_2Cl_2/MeOH)

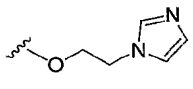
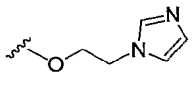
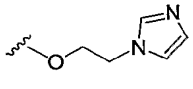
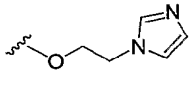
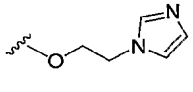
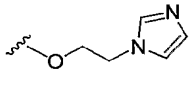
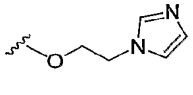
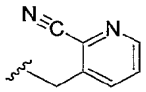
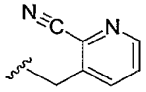
30	H	H		D, AJ	$(M+H)^+$ 404 R_f = 0.40 (94/6 CH_2Cl_2/MeOH)
31	H	H		D, AJ	$(M+H)^+$ 420 R_f = 0.28 (94/6 CH_2Cl_2/MeOH)
32	H	H		D, AJ	$(M+H)^+$ 417 R_f = 0.48 (94/6 CH_2Cl_2/MeOH)
33	H	H		D, AJ	$(M+H)^+$ 421 R_f = 0.37 (94/6 CH_2Cl_2/MeOH)
34	H	H		O, D	$(M+H)^+$ 414 R_f = 0.18 (94/6 CH_2Cl_2/MeOH)
35	F	H		O, D	$(M+H)^+$ 432 R_f = 0.24 (94/6 CH_2Cl_2/MeOH)
36	H		H	Ref.[c]	$(M+H)^+$ 458 R_f = 0.24 (94/6 CH_2Cl_2/MeOH)
37	H	H		P, E	$(M+H)^+$ 414 R_f = 0.26 (94/6 CH_2Cl_2/MeOH)
38	H	H		P, E	$(M+H)^+$ 414 R_f = 0.26 (94/6 CH_2Cl_2/MeOH)

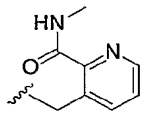
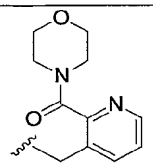
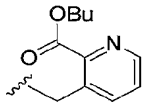
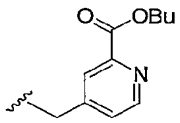
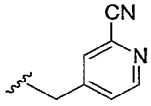
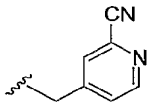
39	F	H		P, E	$(M+H)^+$ 432 R_f = 0.38 (94/6 CH_2Cl_2/MeOH)
40	H	H		P, E	$(M+H)^+$ 414 R_f = 0.34 (94/6 CH_2Cl_2/MeOH)
41	F	H		P, E, Q	$(M+H)^+$ 418 R_f = 0.36 (94/6 CH_2Cl_2/MeOH)
42	H	H		P, E, Q	$(M+H)^+$ 400 R_f = 0.32 (94/6 CH_2Cl_2/MeOH)
43	H	H		P, E, Q	$(M+H)^+$ 400 R_f = 0.21 (94/6 CH_2Cl_2/MeOH)
44	F	H		P, E, Q	$(M+H)^+$ 418 R_f = 0.37 (94/6 CH_2Cl_2/MeOH)
45	F	H		P, E, Q	$(M+H)^+$ 418 R_f = 0.43 (94/6 CH_2Cl_2/MeOH)
46	H	H		P, E, Q	$(M+H)^+$ 400 R_f = 0.21 (94/6 CH_2Cl_2/MeOH)
47	H	OMe		F, H, Q	$(M+H)^+$ 430 R_f = 0.09 (94/6 CH_2Cl_2/MeOH)

48	H	OMe		F, H, Q	$(M+H)^+$ 430 R_f = 0.14 (94/6 CH_2Cl_2/MeOH)
49	F	OMe		F, H, Q	$(M+H)^+$ 448 R_f = 0.19 (96/4 CH_2Cl_2/MeOH)
50	F	OMe		F, H, Q	$(M+H)^+$ 448 R_f = 0.18 (96/4 CH_2Cl_2/MeOH)
51	H	OMe		R, S, E	$(M+H)^+$ 447 R_f = 0.18 (94/6 CH_2Cl_2/MeOH)
52	H	Me		R, S, E	$(M+H)^+$ 431 R_f = 0.09 (94/6 CH_2Cl_2/MeOH)
53	F	Me		R, S, E	$(M+H)^+$ 449 R_f = 0.51 (9/1 EtOAc/MeOH)
54	H	H		T, U, D, V	$(M+H)^+$ 418 R_f = 0.12 (92/8 CH_2Cl_2/MeOH)
55	H	H		W, E	$(M+H)^+$ 389 t_R 1.65in [b]
56	F	H		W, E	$(M+H)^+$ 407 t_R 1.75 min [b]

57	H	OCH_3		W, E	$(M+H)^+$ 419 t_R 1.69 min [b]
58	F	OCH_3		W, E	$(M+H)^+$ 437 t_R 1.72 min [b]
59	H		H	W, E	$(M+H)^+$ 389 t_R 1.08 min [b]
60	F		H	W, E	$(M+H)^+$ 407 t_R 1.50 min [b]
61	H	H		Commercial	$(M+H)^+$ 418 R_f = 0.10 (83/17 EtOAc/Hex)
62	H	H		Y, Z, D	$(M+H)^+$ 419 t_R 1.92 min [b]
63	H	Cl		Y, Z, D	$(M+H)^+$ 453 R_f = 0.80 (4/1 CH_2Cl_2/MeOH)
64	H	H		Y, Z, D	$(M+H)^+$ 513 t_R 2.61 min [b]
65	H	H		Commercial	$(M+H)^+$ 376 t_R 2.03 min.[b]

66	H	H		Ref.[c]	$(M+H)^+$ 402 t_R 1.64 min.[b]
67	H	H		AA,H,P,E	$(M+H)^+$ 444 t_R 2.39 min.[b]
68	Br		H	AF	$(M+H)^+$ 478 t_R 1.98 min.[b]
69	CH_3		H	AF	$(M+H)^+$ 414 t_R 1.80 min.[b]
70	H		H	AB,P,D	$(M+H)^+$ 416 t_R 1.85 min.[b]
71	H		H	AB,P,D	$(M+H)^+$ 418 t_R 2.30 min.[b]
72	F		H	AB,P,D	$(M+H)^+$ 436 t_R 2.38 min.[b]
73	H	H		AC, AD, AE, D	$(M+H)^+$ 417 t_R 1.84 min.[b]
74	F	H		AC, AD, AE, D	$(M+H)^+$ 435 t_R 1.75 min.[b]

75	H	H		Y, Z, D	$(M+H)^+$ 419 t_R 1.68 min.[b]
76	F	H		Y, Z, D	$(M+H)^+$ 437 R_f = 0.26 (9/1 CH_2Cl_2/MeOH)
77	CH_3	H		Y, Z, D	$(M+H)^+$ 453 R_f = 0.41 (85/15 CH_2Cl_2/MeOH)
78	H	OMe		Y, Z, D	$(M+H)^+$ 449 t_R 1.65 min.[b]
79	F	OMe		Y, Z, D	$(M+H)^+$ 467 t_R 1.50 min.[b]
80	H	Me		Y, Z, D	$(M+H)^+$ 433 t_R 1.53 min.[b]
81	F	Me		Y, Z, D	$(M+H)^+$ 451 t_R 1.81 min.[b]
82	H		H	AG, D	$(M+H)^+$ 425 t_R 2.38 min.[b]
83	F		H	AG, D	$(M+H)^+$ 443 t_R 2.33 min.[b]

84	F		H	AG, AH, AI, D	$(M+H)^+$ 475 t_R 2.06 min.[b]
85	H		H	AG, AH, AI, D	$(M+H)^+$ 513 t_R 1.93 min.[b]
86	H		H	AG, AH, D[d]	$(M+H)^+$ 500 t_R 2.53 min.[b]
87	H		H	AG, AH, D[d]	$(M+H)^+$ 500 R_f = 0.25 [5% (2N NH_3 in MeOH)/CH_2Cl_2]
88	H		H	AG, D	$(M+H)^+$ 425 R_f = 0.25 [5% (2N NH_3 in MeOH)/CH_2Cl_2]
89	F		H	AG, D	$(M+H)^+$ 443 R_f = 0.25 [5% (2N NH_3 in MeOH)/CH_2Cl_2]

[a]The structures of the final compounds were confirmed by 1H NMRspectroscopy and the spectra were consistent with the desired chemical structures.

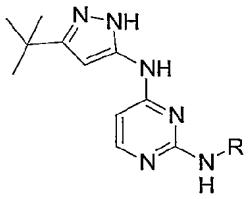
[b]Analytical HPLC were obtained using a Gilson HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (50 x 4.6 mm, 12μm). The eluents were A: acetonitrile w/0.1% TFA and B: H_2O w/0.1% TFA. Gradient elution from 10% B to 90% over 4 min at a flowrate of 4.0 mL/min was used with an initial hold of 0.5 min and a final hold at 90% B of 0.5 minutes. Total run time was 5 min.

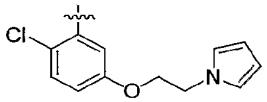
[c]Preparation of compounds can be found in patent application WO0042012.

[d]*n*-Butyl derivatives were formed under the reaction conditions during the coupling

(general method C) of the aniline sidechain to the core.

Table 2. Other Compounds Prepared by Parallel Methods B and C.

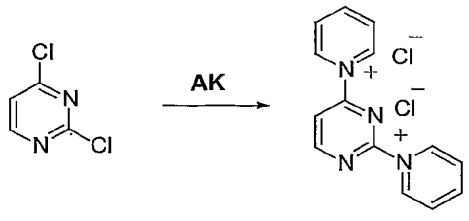


Entry	R	Preparation of Aniline Sidechain	Characterization[a]
90		Y, Z, E	$(M+H)^+$ 453 t_R 1.62 min.[b]

[a]The structures of the final compounds were confirmed by 1H NMRspectroscopy and the spectra were consistent with the desired chemical structures.

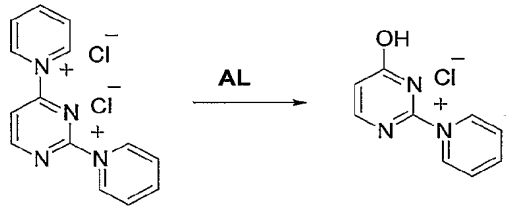
[b]Analytical HPLC were obtained using a Gilson HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (50 x 4.6 mm, 12μm). The eluents were A: acetonitrile w/0.1% TFA and B: H_2O w/0.1% TFA. Gradient elution from 10% B to 90% over 4 min at a flowrate of 4.0 mL/min was used with an initial hold of 0.5 min and a final hold at 90% B of 0.5 minutes. Total run time was 5 min.

Method AK. Preparation of 1-[2-(1-pyridiniumyl)-4-pyrimidinyl]pyridinium dichloride



A solution of 2,4-dichloropyrimidine (84.6 g, 567.9 mmol) in anhydrous pyridine (2.5 L) was heated slowly to reflux over 2 h with mechanical stirring and kept at reflux for 10 min. Over the course of the reaction a thick precipitate formed which became pink in color. The reaction was cooled to ambient temperature over 24 h, then the solid filtered through a coarse sintered glass funnel. The cake washed with copious amounts of ether then dried in vacuo to give the product as a light purple / brown fluffy solid in 99% yield (173.3 g, 564.2 mmol). ^{1}H NMR (300 MHz, DMSO) δ 10.33 (2H, d, J = 6.9 Hz), 10.18 (2H, d, J = 7.2 Hz), 9.78 (1H, d, J = 5.1 Hz), 9.07 and 9.02 (2H, t overlapping, J = 6.0 and 7.8 Hz), 8.95 (1H, d, J = 5.4 Hz), 8.49 (4H, m).

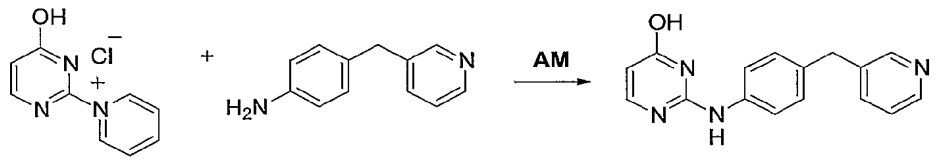
Method AL. Preparation of 1-(4-hydroxy-2-pyrimidinyl)pyridinium chloride



A solution of 1-[2-(1-pyridiniumyl)-4-pyrimidinyl]pyridinium dichloride (100 g, 325.5 mmol) in 0.33 M $NaHCO_3$ solution (109.4 g $NaHCO_3$ in 3.91 L dH_2O) was stirred at 23 °C for 24 h. The brown solution slowly evolved CO_2 (final reaction pH after this time = 7-7.5). The reaction was concentrated by rotary evaporation at 6 mm vacuum at 30 °C, and the crude brown sludge (still containing water) was suspended in methanol and coated on silica gel (700 ml) by concentration in vacuo. The silica-coated crude material was then purified on a plug of silica gel (1 L), eluting with a gradient of 100% CH_3CN (2 L) → 5% MeOH/CH_3CN (1 L) → 10% MeOH/CH_3CN (1 L) → 20% MeOH/CH_3CN (6 L) → 50% MeOH/CH_3CN (1 L) → 50% MeOH/CH_3CN (2 L). The fractions containing product were pooled and concentrated in vacuo to give a brown solid. This was triturated in MeOH (700 ml) with water (300 ml) and the insoluble salts filtered off and washed with MeOH. The filtrate was again coated on silica gel (300 ml) and the column purification repeated as above to give an amber oil/solid. This was again suspended in MeOH/water (2:1) and concentrated until a precipitate formed. The salts were again filtered off and washed with CH_3CN and acetone.

The filtrate was concentrated in vacuo to a brown gum, which solidified after drying in vacuo under P_2O_5. The solid was pulverized with a mortar and pestle then suspended in acetone (1 L), sonicated, and filtered washing with acetone. The product was obtained as a light tan solid in 65% yield (44.04 g, 210.1 mmol) after drying in vacuo under P_2O_5 for 24 h. TLC: *Rf* = 0.40 (33% MeOH/CH_2Cl_2); *Rf* = 0.20 (33% MeOH/CH_2Cl_2 with 1% water); MS (ESI-MS) 174 $[M+H]^+$; ^1H NMR (300 MHz, DMSO) δ 9.89 (2H, d, *J* = 6.9 Hz), 8.84 (1H, t, *J* = 7.5 Hz), 8.41 (1H, d, *J* = 5.7 Hz), 8.29 (2H, t, *J* = 7.2 Hz), 6.79 (1H, d, *J* = 6.0 Hz).

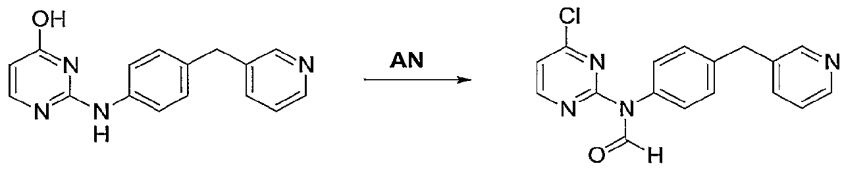
Method AM. Preparation of 2-{[4-(3-pyridinylmethyl)phenyl]amino}-4-pyrimidinol



A suspension of 1-(4-hydroxy-2-pyrimidinyl)pyridinium chloride (3.413 g, 16.28 mmol) and 4-(3-pyridinylmethyl)aniline (3.00 g, 16.28 mmol) in anhydrous *n*-BuOH (100 ml) was stirred under argon. To this was added concentrated HCl (4.07 ml, 48.84 mmol) and the brown suspension stirred at 90 °C (internal temp.) for 1 h (solids dissolve). More 1-(4-hydroxy-2-pyrimidinyl)pyridinium chloride (2.00 g, 9.54 mmol) was then added. The brown solution was stirred at 90 °C (internal temp.) for 16 h. The solvent was removed by rotary evaporation at 2 mm vacuum and 30 °C, and the oily residue was dried in vacuo. The crude product was dissolved in purified by silica gel chromatography (750 ml silica gel, eluting with a gradient of 100% CH_3CN → 30% H_2O/CH_3CN (streaks off). Fractions containing product were pooled and concentrated in vacuo to give impure product. The silica gel chromatography purification was repeated to give the product as a solid amber foam still containing approx. 10% starting aniline. The semi-crude product was dissolved in 4:1 CH_2Cl_2/DMF (250 ml) and the excess aniline starting material scavanged with PS-NCO (Argonaut) (3.0 g) at ambient temperature for 72 h. The scavanger was filtered off and the solvent removed in vacuo at 35 °C to give the product in 89% yield as the HCl salt (4.57 g, 14.52 mmol). TLC: *Rf* = 0.60 (20% H_2O/CH_3CN); MS (ESI-MS) 279 $[M+H]^+$; ^1H NMR (300 MHz, DMSO) δ 8.83 (1H, d, *J* = 2.1 Hz), 8.73 (1H, d, *J* = 5.7 Hz), 8.34 (1H, d, *J* = 7.8), 7.90 (1H, dd, *J* = 5.7, 8.4 Hz), 7.73 (1H, d, *J* = 6.6 Hz), 7.53 (2H, d, *J* = 8.4 Hz), 7.28 (2H, d,

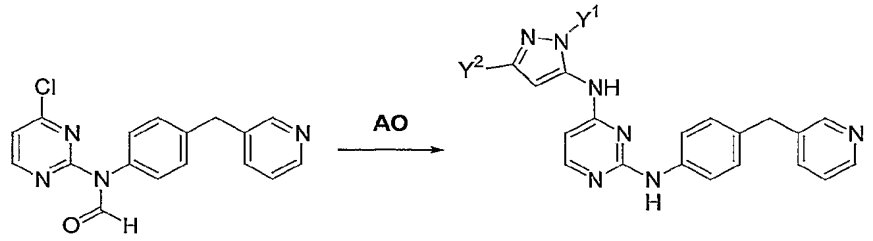
J = 8.4 Hz), 5.85 (1H, d. J = 6.6 Hz), 4.13 (2H, s).

Method AN. Preparation of 4-chloro-2-pyrimidinyl[4-(3-pyridinylmethyl)phenyl]-formamide



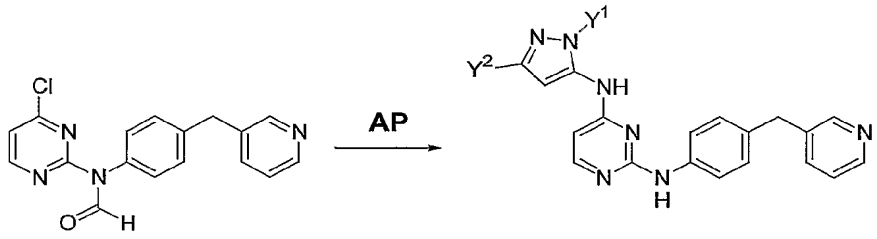
A solution of 2-{[4-(3-pyridinylmethyl)phenyl]amino}-4-pyrimidinol (3.00 g, 9.702 mmol) in anhydrous DMF (80 ml) was added dropwise to stirring phosphorous oxychloride (120 ml) – (40 ml was added in 5 min to achieve an internal temp of 68 °C and the next 40 ml over 25 min to maintain the internal reaction temperature at 66-69 °C). The addition funnel was washed with more DMF (20 ml). TLC analysis after 10 min indicated the absence of starting material. The reaction was cooled to 30 °C over 1 h of stirring, slowly poured into 1.2 L of ice water, and stirred vigorously for 45 min keeping the internal quench temp at 15 °C (external cooling of the flask was necessary). The acidic solution was further quenched by portionwise addition of powdered K_2CO_3 (536 g) over 1 h with vigorous stirring to a final pH of 10 (internal temp. was always kept between 10-20 °C during the quench; vigorous bubbling observed). The still-cold light brown suspension was extracted with EtOAc (2 X 2L), and this was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give an orange oil. This material was dried *in vacuo* at 30 °C to give a solid orange/brown residue. This was purified by a silica gel plug chromatography (100% EtOAc) to give the product as a yellowish oil which crystallized to an amber solid in 69% yield (2.00 g, 6.74 mmol). TLC: Rf = 0.60 (10% H_2O/CH_3CN); MS (ESI-MS): 325.0 $[M+H]^+$; ^1H NMR (300 MHz, DMSO) δ 9.71 (1H, s), 8.58 (1H, d, J = 5.1 Hz), 8.55 (1H, d, J = 1.8), 8.42 (1H, dd, J = 1.2, 4.5 Hz), 7.70 (1H, dt, J = 1.8, 8.1 Hz), 7.45 (1H, d, J = 5.1 Hz), 7.34 (2H, d, J = 8.4 Hz), 7.16 (2H, d. J = 8.1 Hz), 7.32 (1H, obsc. dd), 4.02 (2H, s).

General Method AO. Coupling of substituted 5-amino pyrazoles with 4-chloro-2-pyrimidinyl[4-(3-pyridinylmethyl)phenyl]-formamide using dilute conditions



4-Chloropyrimidine intermediate (1 equiv), aminopyrazole (1.25 equiv), *n*-BuOH (0.15 M), and HCl (concentrated, 1 drop) are combined and heated at 100 °C overnight. The mixture is taken up in CH_2Cl_2 and washed with $NaHCO_3$ before being dried (Na_2SO_4) and concentrated. Purification of the residue by flash silica gel chromatography provides the desired 2,4-diaminopyrimidienes whose structures are confirmed by LC/MS and ^1H NMR.

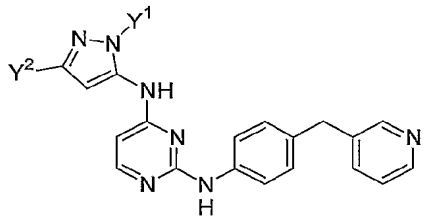
General Method AP. Coupling of substituted 5-amino pyrazoles with 4-chloro-2-pyrimidinyl[4-(3-pyridinylmethyl)phenyl]-formamide using concentrated conditions

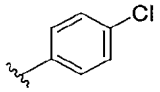
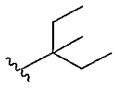


4-Chloropyrimidine intermediate (1 equiv), aminopyrazole (1.25 equiv), and HCl (concentrated, 1 drop) are combined and heated at 100 °C overnight. The mixture is taken up in CH_2Cl_2 and washed with $NaHCO_3$ before being dried ($MgSO_4$) and concentrated. Purification of the residue by flash silica gel chromatography provided the desired 2,4-diaminopyrimidienes whose structures were confirmed by LC/MS and ^1H NMR.

The compounds of examples 91-99 are prepared by general method AO or AP where a 4-chloropyrimidine (prepared by methods AK-AN) is reacted with an amino pyrazole (prepared by general method A):

Table 3. Compounds Prepared by general method AO or AP



Entry	Y^1	Y^2	Preparation of Aniline Sidechain	Characterization[a]
91	H	Me	AO[c]	$(M+H)^+$ 358 R_f = 0.63 (8/2 CH_2Cl_2/MeOH)
92	H		AO[c]	$(M+H)^+$ 454 R_f = 0.72 (8/2 CH_2Cl_2/MeOH)
93	Me	*tert*-butyl	AO[c]	$(M+H)^+$ 414 R_f = 0.28 (19/1 CH_2Cl_2/MeOH)
94	H	*tert*-pentyl	AP	$(M+H)^+$ 414 t_R 1.71 min.[b]
95	H		AO	$(M+H)^+$ 428 t_R 1.74 min.[b]
96	H	Cyclopropyl	AP	$(M+H)^+$ 384 t_R 1.08 min.[b]
97	H	CF_3	AP	$(M+H)^+$ 412 t_R 1.61 min.[b]

98	H	cyclopentyl	AP	$(M+H)^+$ 412 t_R 1.74 min.[b]
99	H	neopentyl	AP	$(M+H)^+$ 414 t_R 1.78 min.[b]

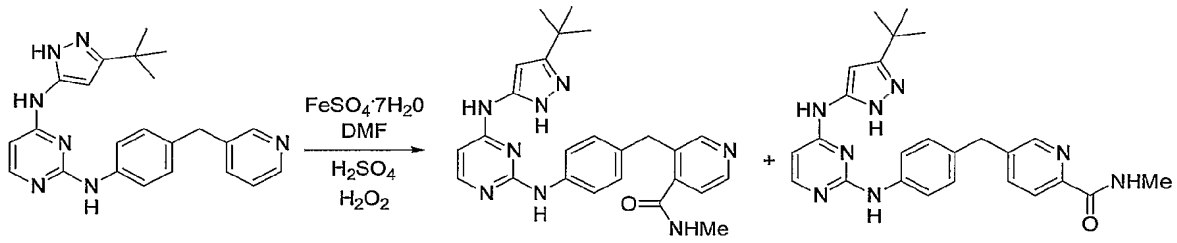
[a]The structures of the final compounds were confirmed by 1H NMR spectroscopy and the spectra were consistent with the desired chemical structures.

[b]Analytical HPLC were obtained using a Gilson HPLC equipped with a quaternary pump, a variable wavelength detector set at 254 nm, a YMC pro C-18 column (50 x 4.6 mm, 12μm). The eluents were A: acetonitrile w/0.1% TFA and B: H_2O w/0.1% TFA. Gradient elution from 10% B to 90% over 4 min at a flowrate of 4.0 mL/min was used with an initial hold of 0.5 min and a final hold at 90% B of 0.5 minutes. Total run time was 5 min.

[c]Pyrazole is commercially available.

Example 100. Preparation of 3-[4-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-2-pyrimidinyl}amino)benzyl]-*N*-methylisonicotinamide

Example 101. Preparation of 5-[4-({4-[(3-*tert*-butyl-1*H*-pyrazol-5-yl)amino]-2-pyrimidinyl}-amino)benzyl]-*N*-methyl-2-pyridinecarboxamide



100 101

To a stirring solution of *N*-(3-*tert*-butyl-1*H*-pyrazol-5-yl)-*N*-(2-{[4-(3-pyridinylmethyl)-phenyl]amino}-4-pyrimidinyl)amine (195 mg, 0.488 mmol), and $FeSO_4.7H_2O$ (68 mg, 0.244 mmol) in *N*-methylformamide (10 ml) was added concentrated H_2SO_4 (96 mg, 0.976 mmol) followed by 30% aqueous H_2O_2 (0.15 ml, 1.464 mmol). An exotherm of +5 °C was

observed, and the reaction is stirred at an ambient temperature at 30 °C for 1 h. Additional 30% aqueous H_2O_2 was added (0.45 ml, 4.39 mmol) and the reaction stirred an additional 3 h at 25 °C. The reaction was quenched with saturated K_2CO_3 (75 ml), and extracted with EtOAc (3 X 150 ml). The combined organics were dried (Na_2SO_4) and the solvent removed in vacuo. The crude product, containing three regiosiomers, was purified by silica gel chromatography (100% CH_3CN → 10% H_2O/CH_3CN gradient) to afford two fractions which were treated separately:

The first fraction, which contained two isomers, was further separated by reverse-phase prep-HPLC chromatography to furnish example 101, the second eluting isomer. Subsquent crystallization of example 101 to a white solid over 2 months from the slowly-evaporating HPLC fractions provided the product in 6% yield (12.5 mg, 0.0273 mmol). TLC: *Rf* = 0.40 (5% H_2O/CH_3CN); MS (ESI-MS) 457 $[M+H]^+$; ^1H NMR (300 MHz, DMSO) δ 12.27 (1H, b s), 10.90 (1H, b s), 9.66 (1H, b s), 8.64 (1H, d, *J* = 4.2 Hz), 8.45 (1H, d, *J* = 3.9 Hz), 7.69 (1H, d, *J* = 7.5 Hz), 7.46 (1H, dd. *J* = 5.1, 8.1 Hz), 7.42 (2H, d, *J* = 9.3 Hz), 7.24 (2H, d, *J* = 8.1 Hz), 6.42 (1H, b s), 6.19 (1H, b s), 4.39 (2H, s), 2.76 (3H, d, *J* = 4.5 Hz), 1.13 (9H, s).

The second fraction containing example 100 was triturated with CH_2Cl_2/hexane to give product, 100, as a white solid in 15% yield (33 mg, 0.0723 mmol). TLC: *Rf* = 0.20 (5% H_2O/CH_3CN); MS (ESI-MS) 457 $[M+H]^+$; ^1H NMR (300 MHz, DMSO) δ 11.90 (1H, b s), 9.46 (1H, b s), 8.99 (1H, b s), 8.46 (1H, s), 8.42 (1H, d, *J* = 5.1 Hz), 8.38 (1H, d, *J* = 5.1 Hz), 7.90 (1H, d, *J* = 5.4 Hz), 7.57 (2H, d, *J* = 8.7 Hz), 7.22 (1H, d, *J* = 4.8 Hz), 7.02 (2H, d, *J* = 8.1 Hz), 6.34 (1H, b s), 6.17 (1H, b s), 3.97 (2H, s), 2.69 (3H, d, J = 4.2 Hz), 1.19 (9H, s).

Assays for testing the activity of the compounds

This section describes assays that can be used to characterize compounds of the invention, e.g., src kinase activity assays; assays for testing the activity of compounds on kinases other than src; and assays for testing the activity of compounds on cell proliferation and differentiation.

A preferred method for measuring src kinase activity (a "src biochemical assay") uses ATP (5 μM/well) mixed with biotinylated poly-GAT substrate (10 nM/well), Streptavidin-APC (15 nM/well) and European-labeled anti-phosphotyrosine antibody (2.5 nM/well). 10 μl of a mixture of these components is added to each well of a black 96-well plate, with or without test compound (5 μl desired concentration of compound in DMSO). 75 μl of assay

buffer (50 mM HEPES pH 7.5, 0.1 mM EDTA, 0.015% BRIJ 35 solution, 0.1 mg/mL BSA, 0.1% beta-mercaptoethanol, 10 mM magnesium chloride) is then added to each well. Last, the src kinase (0.1 units/well) (Upstate Biotech, Lake Placid, NY) is added (10 µl) to a final volume of 100 µl. After 3-hour incubation at room temperature, plates are read on Wallac 1420 Victor Multilabel Counter (Perkin Elmer™ Life Sciences, Boston, MA) at 665 and 615 nm. A specific signal is the ratio of the value of the signal at 665 and the value of the signal at 615 multiplied by 10,000 (i.e., (signal at 665/signal at 615) x 10,000). Compounds that cause the specific signal to decrease inhibit the kinase activity of src. Percent inhibitions and/or IC_{50} values can then calculated based on specific signals from wells that have no compound added, i.e., zero percent inhibition.

A specific signal is the ratio of the value of the signal at 665 and the value of the signal at 615 multiplied by 10,000 (i.e., (signal at 665/signal at 615) x 10,000). Compounds that cause the specific signal to decrease inhibit the kinase activity of src. Percent inhibitions and/or IC_{50} values can then calculated based on specific signals from wells that have no compound added, i.e., zero percent inhibition.

Compounds of examples 1, 3-4, 7-8, 11, 15, 20-23, 25-29, 32-35, 41-50, 54-58, 63, 70, 73-76, 78-82, 88, 96, 98-99 show an IC_{50} less than 500 nM in the src biochemical assay. Compounds of examples 6, 12-14, 16-19, 24, 52-53, 62, 64, 66, 69, 71-73, 77, 83, 91, 94-95 show an IC_{50} greater than 500 nM but less than 1.0 µM and/or percent inhibition greater than 50 in the src biochemical assay. Compounds of examples 2, 5, 9-10, 30-31, 36-40, 51, 59-61, 65, 67-68, 84-87, 89-90, 92-93, 97, 100-101 show an IC_{50} greater than 1 µM and/or percent inhibition less than 50 but greater than 30 in the src biochemical assay.

It will be understood by a person of skill in the art that modified versions of the src biochemical assay described above can be conducted. These alternative assays can also be used to test the inhibitory activity of compounds of the invention or analogs or derivatives thereof.

The assay can also be adapted to determine the inhibitory activity of compounds towards kinases other than src kinases. For example, the src kinase enzyme in the above assay can be replaced with another kinase. When testing the inhibitory activity on kinases that are not tyrosine kinases, the antibody in the assay may also have to be replaced with an antibody that is specific for the phosphorylated residue, which has been phosphorylated by the kinase.

The effect of compounds on cell proliferation can be determined, e.g., by incubating cells with varying amounts of the compounds and counting the cells over time. Viable cells can be counted by staining the cells with a specific dye, e.g., Trypan Blue, according to methods well known in the art. Other methods include measuring the incorporation of a labeled molecule into DNA or RNA or protein of cells. For example, cell proliferation is often measured by ^{3}H thymidine or 5-bromodeoxyuridine incorporation assays, also well known in the art. An increase in ^{3}H thymidine or 5-bromodeoxyuridine incorporation in cells incubated with a test compound that is similar to that in cells non incubated with the test compound indicates that the test compound is essentially not inhibiting the proliferation of the cells. On the contrary, a lower ^{3}H thymidine or 5-bromodeoxyuridine incorporation in cells incubated with a test compound relative to cells that were not treated with the test compound indicates that the test compound inhibits cell proliferation.

The effect of a compound on cell differentiation can be determined by visualization of the cells after having been contacted with the compound, preferably by comparison with cells which have not been contacted with the compound. The differentiation of certain cells is visible by the naked eye (e.g., that of 3T3L1 cells), whereas that of other cells may require the use of a microscope. Specific dyes can also be used to evaluate the state of differentiation of cells. Cell differentiation can also be monitored by measuring the expression level of certain genes, whose expression is known to vary during differentiation of the cells.

The effect of a compound on a cell can be determined in a cell that contains an abnormal kinase, e.g., a mutated kinase gene, or a cell which over-expresses a kinase. For example the cell can be a cell expressing a mutated form of a tyrosine kinase, e.g., src kinase, thereby transforming the cell. The cell can also be a cell that has an abnormal proliferation which is not caused by an abnormal activity or level of a kinase. Cells that can be used for testing compounds of the invention include cell lines and primary cell cultures. Numerous cell lines that are transformed, e.g., by over-expression of a proto-oncogene, which encodes, e.g., a kinase, are available, e.g., from the American Type Culture Collection (ATCC, 10801 University Blvd., Manassas, Virginia 20110. Cell lines over-expressing a gene, e.g., a kinase, can be prepared by transient, or preferably, stable transfection of cells with an expression plasmid containing the gene, according to methods well known in the art. Nucleic acids for use in transforming cells, e.g., nucleic acids encoding kinases, are also

publicly available or can readily be obtained. Cell lines can also be obtained from transgenic animals, e.g., animals overexpressing a kinase or expressing a mutated kinase. For example, MG 1361 is a breast carcinoma cell line obtained from the MMTV-neu transgenic mouse (Sacco *et al.*, Breast Cancer Res. Treat., 47:171-180 (1998)). Primary cell cultures can be established from biopsies obtained from patients, e.g., patients having cancer.

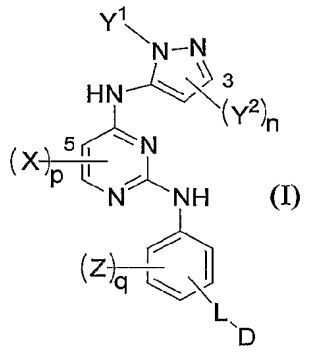
The present invention also provides methods of testing a compound (e.g., the candidate drug) for its inhibition of src, its antiproliferative effect, its effect on cell differentiation and/or its toxicity on normal or wild-type cells in animals, e.g., transgenic animals, e.g., mice. Transgenic mice are produced that express a transforming agent (e.g., a growth factor receptor) under the control of a promoter, e.g., a tissue specific promoter. Such mice develop carcinomas that have genetic and pathological features that closely resemble human cancers. For example, mice expressing viral polyoma middle T antigen under the control of the MMTV promoter produces highly metastatic mammary tumors with elevated c-src kinase activity (Guy *et al.* (1994) Genes and Dev. 8:23). Nude mice in which tumor cell lines have been administered can also be used. For example, breast cancer cell lines over-expressing c-src can be administered to nude mice (*see, e.g.,* Biscardi *et al.* (1998) Mol. Carcinog. 21: 261). The ability of the compound to inhibit tumor formation or growth is then ascertained. In one embodiment the size of the tumor is monitored by determining the tumor size and/or weight. The compounds can be administered by a variety of ways including orally, subcutaneously, or intraperitoneally. Generally, at least two groups of animals are used in the assay, with at least one group being a control group which is administered the administration vehicle without the compound.

An animal model for osteoporosis that can be used for testing the activity of compounds is described, e.g., in Missbach *et al.* (1999) Bone 24:437 and in Sims *et al.* (1999) J. Bone Miner. Res. 14: S183.

Other embodiments of the invention will be apparent to the skilled in the art from a consideration of this specification or practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with the true scope and spirit of the invention being indicated by the following claims.

We claim:

1. A compound of the formula (I)



(I)

wherein

Y^1 represents H or C_{1-4} alkyl;

Y^2 represents CF^3, C_{1-6} alkyl, C_{3-6} cycloalkyl, or phenyl optionally substituted with halogen, C_{1-4} alkyl, or C_{1-4} alkoxy;

n is 0, 1, or 2;

X represents halogen or C_{1-4} alkyl;

p is 0, 1, or 2;

Z represents halogen, C_{1-4} alkyl, or C_{1-4} alkoxy;

q is 0, 1, or 2;

L represents

a chemical bond,

C_{1-4} alkylene,

O,

$O(C_{1-4}$ alkylene),

$CH(C_{1-6}$ alkoxy),

$S(O)_{0-2}$,

$S(O)_{0-2}(C_{1-4}$ alkylene),

$(C_{1-4}$ alkylene$)S(O)_{0-2}$,

$NH(C_{1-4}$ alkylene),

C(O), or

$C(O)$-$(C_{1-4}$ alkylene);

D represents

pyridinyl,

imidazolyl,

thiazolyl,

pyrrolyl,

thienyl,

pyrazolyl,

furyl,

thiadiazolyl,

oxazolyl, or

benzimidazolyl;

said pyridinyl and benzimidazolyl groups D each being optionally substituted by up to three substituents independently selected from C_{1-4} alkyl, OH, C_{1-4} alkoxy, CN, NR^1R^2, $C(O)NR^1R^2$, halogen, and $CO_2(C_{1-6}$ alkyl);

wherein

R^1 and R^2 are independently selected from H, C_{1-4} alkyl, and C_{3-6} cycloalkyl, or

R^1 and R^2 are joined to form a 5-6 membered saturated heterocycle

wherein

Q represents O, $S(O)_{0-2}$, N-Y^1, or $C(Y^1)_2$;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 wherein

Y^1 represents H.

3. A compound of claim 1 wherein

Y^2 represents CF^3, C_{1-6} alkyl, C_{3-6} cycloalkyl, or phenyl optionally substituted with

halogen, C_{1-4} alkyl, or C_{1-4} alkoxy; and
n is 1 or 2.

4. A compound of claim 1 wherein
Y^2 represents C_{1-6} alkyl, C_{3-6} cycloalkyl, or phenyl optionally substituted with halogen, C_{1-4} alkyl, or C_{1-4} alkoxy; and
n is 1 or 2.

5. A compound of claim 1 wherein
Y^2 represents C_{1-6} alkyl or C_{3-6} cycloalkyl; and
n is 1 or 2.

6. A compound of claim 1 wherein
X represents Cl, F, or C_{1-4} alkyl; and
p is 0 or 1.

7. A compound of claim 1 wherein
X represents F or C_{1-4} alkyl; and
p is 0 or 1.

8. A compound of claim 1 wherein
X represents F; and
p is 0 or 1.

9. A compound of claim 1 wherein
Z represents Cl, F, C_{1-4} alkyl, or C_{1-4} alkoxy; and
q is 0, 1, or 2.

10. A compound of claim 1 wherein
Z represents F, C_{1-4} alkyl, or C_{1-4} alkoxy; and

q is 0 or 1.

11. A compound of claim 1 wherein

Z represents C_{1-4} alkyl, or C_{1-4} alkoxy; and

q is 0 or 1.

12. A compound of claim 1 wherein

L represents

a chemical bond,

C_{1-4} alkylene,

$O(C_{1-4}$ alkylene),

$CH(C_{1-6}$ alkoxy),

$S(O)_{0-2}(C_{1-4}$ alkylene),

$(C_{1-4}$ alkylene$)S(O)_{0-2}$,

$NH(C_{1-4}$ alkylene), or

$C(O)$-$(C_{1-4}$ alkylene).

13. A compound of claim 1 wherein

L represents

a chemical bond,

C_{1-4} alkylene,

$O(C_{1-4}$ alkylene),

$S(O)_{0-2}(C_{1-4}$ alkylene),

$(C_{1-4}$ alkylene$)S(O)_{0-2}$, or

$NH(C_{1-4}$ alkylene).

14. A compound of claim 1 wherein

L represents

C_{1-4} alkylene,

$O(C_{1-4}$ alkylene), or

$NH(C_{1-4}$ alkylene).

15. A compound of claim 1 wherein

D represents

pyridinyl,

imidazolyl,

thiazolyl,

pyrrolyl,

pyrazolyl, or

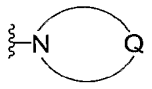
benzimidazolyl.

said pyridinyl and benzimidazolyl groups D each being optionally substituted by up to three substituents independently selected from C_{1-4} alkyl, OH, C_{1-4} alkoxy, CN, NR^1R^2, $C(O)NR^1R^2$, halogen, and $CO_2(C_{1-6}$ alkyl);

wherein

R^1 and R^2 are independently selected from H, C_{1-4} alkyl, and C_{3-6} cycloalkyl, or

R^1 and R^2 are joined to form a 5-6 membered saturated heterocycle



wherein

Q represents O, $S(O)_{0-2}$, $N\text{-}Y^1$, or $C(Y^1)_2$.

16. A compound of claim 1 wherein

D represents

pyridinyl,

imidazolyl,

thiazolyl,

pyrrolyl,

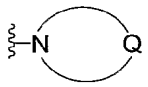
pyrazolyl, or

said pyridinyl group D being optionally substituted by up to three substituents independently selected from C_{1-4} alkyl, OH, C_{1-4} alkoxy, CN, NR^1R^2, $C(O)NR^1R^2$, halogen, and $CO_2(C_{1-6}$ alkyl);

wherein

R^1 and R^2 are independently selected from H, C_{1-4} alkyl, and C_{3-6} cycloalkyl, or

R^1 and R^2 are joined to form a 5-6 membered saturated heterocycle



wherein

Q represents O, $S(O)_{0-2}$, N-Y^1, or $C(Y^1)_2$.

17. A compound of claim 1 wherein

D represents

pyridinyl, or

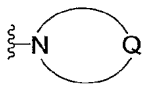
imidazolyl,

said pyridinyl group D being optionally substituted by up to three substituents independently selected from C_{1-4} alkyl, OH, C_{1-4} alkoxy, CN, NR^1R^2, $C(O)NR^1R^2$, halogen, and $CO_2(C_{1-6}$ alkyl);

wherein

R^1 and R^2 are independently selected from H, C_{1-4} alkyl, and C_{3-6} cycloalkyl, or

R^1 and R^2 are joined to form a 5-6 membered saturated heterocycle



wherein

Q represents O, $S(O)_{0-2}$, N-Y^1, or $C(Y^1)_2$.

18. A compound of claim 1 wherein

Y^1 represents H or C $_{1-4}$ alkyl;

Y^2 represents CF^3, C_{1-6} alkyl, C_{3-6} cycloalkyl, or phenyl optionally substituted with halogen, C_{1-4} alkyl, or C_{1-4} alkoxy;

n is 1 or 2;

X represents Cl, F, or C_{1-4} alkyl;

p is 0 or 1,

Z represents Cl, F, C_{1-4} alkyl, or C_{1-4} alkoxy;

q is 0, 1, or 2;

L represents

a chemical bond,

C_{1-4} alkylene,

$O(C_{1-4}$ alkylene),

$CH(C_{1-6}$ alkoxy),

$S(O)_{0-2}(C_{1-4}$ alkylene),

$(C_{1-4}$ alkylene$)S(O)_{0-2}$,

$NH(C_{1-4}$ alkylene), or

$C(O)$-$(C_{1-4}$ alkylene);

D represents

pyridinyl,

imidazolyl,

thiazolyl,

pyrrolyl,

pyrazolyl, or

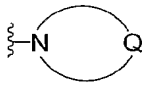
benzimidazolyl;

said pyridinyl and benzimidazolyl groups D each being optionally substituted by up to three substituents independently selected from C_{1-4} alkyl, OH, C_{1-4} alkoxy, CN, NR^1R^2, $C(O)NR^1R^2$, halogen, and $CO_2(C_{1-6}$ alkyl);

wherein

R^1 and R^2 are independently selected from H, C_{1-4} alkyl, and C_{3-6} cycloalkyl, or

R^1 and R^2 are joined to form a 5-6 membered saturated heterocycle



wherein

Q represents O, $S(O)_{0-2}$, N-Y^1, or $C(Y^1)_2$.

19. A compound of claim 1 wherein

Y^1 represents H;

Y^2 represents C_{1-6} alkyl, C_{3-6} cycloalkyl, or phenyl optionally substituted with halogen, C_{1-4} alkyl, or C_{1-4} alkoxy;

n is 1 or 2;

X represents F or C_{1-4} alkyl;

p is 0 or 1,

Z represents F, C_{1-4} alkyl, or C_{1-4} alkoxy;

q is 0 or 1,

L represents

a chemical bond,

C_{1-4} alkylene,

$O(C_{1-4}$ alkylene),

$S(O)_{0-2}(C_{1-4}$ alkylene),

$(C_{1-4}$ alkylene$)S(O)_{0-2}$, or

$NH(C_{1-4}$ alkylene);

D represents

pyridinyl,

imidazolyl,

thiazolyl,

pyrrolyl, or

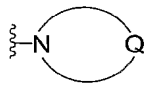
pyrazolyl,

said pyridinyl groups D each being optionally substituted by up to three substituents independently selected from C_{1-4} alkyl, OH, C_{1-4} alkoxy, CN, NR^1R^2, $C(O)NR^1R^2$, halogen, and $CO_2(C_{1-6}$ alkyl);

wherein

R^1 and R^2 are independently selected from H, C_{1-4} alkyl, and C_{3-6} cycloalkyl, or

R^1 and R^2 are joined to form a 5-6 membered saturated heterocycle



wherein

Q represents O, $S(O)_{0-2}$, N-Y^1, or $C(Y^1)_2$.

20. A compound of claim 1 wherein

Y^1 represents H;

Y^2 represents C_{1-6} alkyl or C_{3-6} cycloalkyl;

n is 1 or 2;

X represents F;

p is 0 or 1,

Z represents C_{1-4} alkyl or C_{1-4} alkoxy;

q is 0 or 1;

L represents

C_{1-4} alkylene,

$O(C_{1-4}$ alkylene), or

$NH(C_{1-4}$ alkylene);

D represents

pyridinyl or

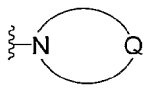
imidazolyl,

said pyridinyl groups D each being optionally substituted by up to three substituents independently selected from C_{1-4} alkyl, OH, C_{1-4} alkoxy, CN, NR^1R^2, $C(O)NR^1R^2$, halogen, and $CO_2(C_{1-6}$ alkyl);

wherein

R^1 and R^2 are independently selected from H, C_{1-4} alkyl, and C_{3-6} cycloalkyl, or

R^1 and R^2 are joined to form a 5-6 membered saturated heterocycle



wherein

Q represents O, $S(O)_{0-2}$, N-Y^1, or $C(Y^1)_2$.

21. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

22. A method of inhibiting Src kinase receptors in a subject comprising contacting said receptors with the compound according to claim 1.

23. A method for treating a disease associated with a src kinase in a subject, comprising administering to said subject a therapeutically effective amount of a compound according to claim 1, such that the disease is treated.

24. The method of claim 23 wherein said disease is cancer or osteoporosis.

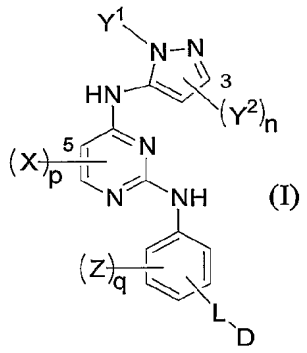
25. A method for treating cancer in a subject, comprising administering to said subject a therapeutically effective amount of a compound according to claim 1, such that the cancer is treated.

26. The method of claim 24, wherein the cancer is selected from the group consisting of breast cancer, colon cancer, pancreatic cancer, lung cancer, neural cancer, esophageal cancer, gastric cancer, melanoma and Kaposi's sarcoma.

27. A method for treating a non-malignant proliferative disease in a subject, comprising administering to said subject a therapeutically effective amount of a compound according to claim 1, such that the non-malignant proliferative disease is treated.

28. A method for treating osteoporosis in a subject, comprising administering to said subject a therapeutically effective amount of a compound according to claim 1, such that the osteoporosis is treated.

29. A method for making a compound of the formula (I)



(I)

wherein

Y^1 represents H or C_{1-4} alkyl;

Y^2 represents CF^3, C_{1-6} alkyl, C_{3-6} cycloalkyl, or phenyl optionally substituted with halogen, C_{1-4} alkyl, or C_{1-4} alkoxy;

n is 0, 1, or 2;

X represents halogen or C_{1-4} alkyl;

p is 0, 1, or 2;

Z represents halogen, C_{1-4} alkyl, or C_{1-4} alkoxy;

q is 0, 1, or 2;

L represents

a chemical bond,

C_{1-4} alkylene,

O,

$O(C_{1-4}$ alkylene),

$CH(C_{1-6}$ alkoxy),

$S(O)_{0-2}$,

$S(O)_{0-2}(C_{1-4}$ alkylene),

(C_{1-4} alkylene)$S(O)_{0-2}$,

$NH(C_{1-4}$ alkylene),

C(O), or

$C(O)$-(C_{1-4} alkylene);

D represents

pyridinyl,

imidazolyl,

thiazolyl,

pyrrolyl,

thienyl,

pyrazolyl,

furyl,

thiadiazolyl,

oxazolyl, or

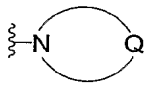
benzimidazolyl;

said pyridinyl and benzimidazolyl groups D each being optionally substituted by up to three substituents independently selected from C_{1-4} alkyl, OH, C_{1-4} alkoxy, CN, NR^1R^2, $C(O)NR^1R^2$, halogen, and $CO_2(C_{1-6}$ alkyl);

wherein

R^1 and R^2 are independently selected from H, C_{1-4} alkyl, and C_{3-6} cycloalkyl, or

R^1 and R^2 are joined to form a 5-6 membered saturated heterocycle

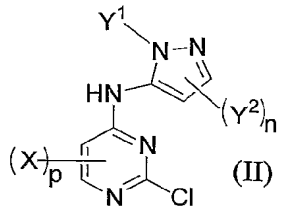


wherein

Q represents O, $S(O)_{0-2}$, N-Y^1, or $C(Y^1)_2$,

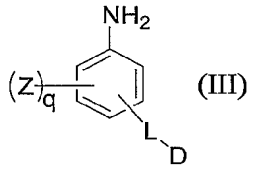
comprising

coupling a compound of formula (II)



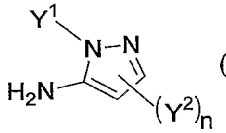
(II)

with a compound of formula (III)

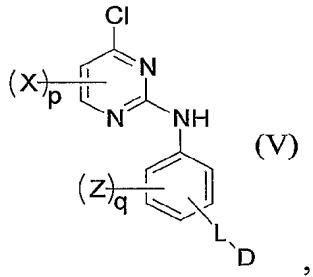

(III)

or

coupling a compound of formula (IV)


(IV)

with a compound of formula (V)


(V)

, to yield a compound of formula (I).

INTERNATIONAL SEARCH REPORT

ational Application No
PCT/US 02/30836

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/506 C07D401/14 C07D403/14 C07D405/14 C07D409/14
C07D413/14 C07D417/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 60816 A (AMGEN INC) 23 August 2001 (2001-08-23) page 72 -page 76; claim 1 page 19, line 13 - line 20	1-29
X	WO 97 19065 A (CELLTECH THERAPEUTICS LTD ;DAVIS PETER DAVID (GB); MOFFAT DAVID FE) 29 May 1997 (1997-05-29) page 77; claim 1 page 1, line 35 -page 2, line 4	1-29
X	WO 01 64656 A (PEARSON STUART ERIC ;PEASE ELIZABETH JANET (GB); ASTRAZENECA UK LT) 7 September 2001 (2001-09-07) page 52 -page 54; claim 1 page 2, line 1 - line 9	1-29

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 November 2002	04/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Fink, D

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/US 02/30836

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 22-28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

ational Application No
PCT/US 02/30836

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0160816 A	23-08-2001	AU 3704101 A	27-08-2001
		WO 0160816 A1	23-08-2001
		US 2002052386 A1	02-05-2002
WO 9719065 A	29-05-1997	AU 7631496 A	11-06-1997
		EP 0862560 A1	09-09-1998
		WO 9719065 A1	29-05-1997
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		US 5958935 A	28-09-1999
WO 0164656 A	07-09-2001	AU 3397901 A	12-09-2001
		WO 0164656 A1	07-09-2001